The role of head size in total hip arthroplasty

Dislocation, wear and cup stability

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“Θέλουνε οι σπουδές λεφτά, θέλουν λεφτά χιλιάδες,
μα εγώ δεν εβοήθησα, μόνο με μαντινάδες”
-γιαγιά Αθηνούλα-

“You don’t burn out from going too fast.
You burn out from going too slow and getting bored”
- Cliff Burton –

ABSTRACT

Large heads are used in total hip arthroplasty, with the aim of reducing the risk of dislocation, but there are concerns related to polyethylene wear, corrosion and cup loosening. Paper I is an observational study that aimed to investigate whether the transition from 28-mm to 32-mm heads and thereafter to 36-mm heads in patients undergoing total hip arthroplasty (THA) after osteoarthritis has been followed by a reduction in dislocation rates in the Nordic countries. The results showed that the use of 32-mm rather than 28-mm heads reduced the risk of revision due to dislocation. A further increase from 32- to 36-mm heads was not associated with any further reduction in the risk of revision due to dislocation. Paper II is an observational study that investigated whether there is a difference in the risk of revision due to dislocation between 2 propensity score matched groups of patients that had received a 36-mm or a 32-mm THA after femoral neck fracture. The results showed no difference. Paper III is a randomized, controlled trial that aimed to compare polyethylene wear, measured with roentgen stereophotogrammetry (RSA), between patients that underwent a THA with the largest possible metal head (36-44 mm) and patients with a 32-mm THA. There was no difference in polyethylene wear. Paper IV aimed to compare whole-blood cobalt, chromium and titanium levels between patients that had randomly received either the largest possible cobalt-chromium head (36-44 mm) or a 32-mm cobalt-chromium head on a titanium stem. Whole-blood ion levels, as an indicator of taper corrosion, were very low and did not differ between the groups. Paper V aimed to investigate whether the increased frictional torques that are generated by the largest possible metal heads (36-44 mm) on highly cross-linked polyethylene bearings would compromise the fixation of cementless cups, compared with 32-mm heads. Using RSA, no difference in cup migration was found.

The thesis concludes that the use of 32-mm heads in routine THA has provided greater stability than 28-mm heads. The use of 36-mm heads did not provide any additional stability. In patients with a femoral neck fracture, the use of 36-mm heads did not provide any additional stability either. In order to achieve even greater stability, even larger heads are probably required. The concerns about polyethylene wear, taper corrosion and cup loosening could not be confirmed by the results of the thesis, but longer-term results are warranted before drawing any definite conclusions about the safety of larger heads.

Keywords: arthroplasty, head, dislocation, wear, corrosion, cup migration
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SAMMANFATTNING PÅ SVENSKA

När total höftprotes inleddes på 60-talet användes ett icke modulärt 22 mm ledhuvud. Sedan dess har ledhuvudstorlek ökat successivt till 28 mm på 90-talet för att sedan ersättas av 32 mm mot slutet av 2010-talet. Numera används framför allt modulära 32 mm ledhuvud som standard och användandet av 36 mm ledhuvud ökar. Den största drivkraften för att använda stora ledhuvud har varit professionens försök att minska risken för dislokation som fortfarande är en av de vanligaste orsakerna till omoperation av en höftprotes. Det som hållit tillbaka utvecklingen av ledhuvudstorlek var användandet av konventionell plast i cupen, som slets med tiden och orsakade benförlust runt protesen, och kunde leda till lossning. När korslänkad plast introducerades på slutet av 90 talet, visade den sig vara mycket mer slitstark än konventionell plast och större modulära ledhuvud började användas i större utsträckning. Detta ledde samtidigt att plasttjockleken blev tunnare vilket skapar en viss oro för genomslitning. Korslänkningen bidrog också till att plasten blev mer spröd på grund av oxidering. Korslänkad plast dopad med vitamin E är en vidareutveckling av första generationens korslänkningsprocess. Vitamin E bidrar till att plasten blir mer motståndskraftig mot oxidering och därmed minskar risken för slitage och plastbrott vilket då skulle tillåta användning av ännu större ledhuvud. Samtidig som användandet av större ledhuvud ökade märktes att höftledsplastik med 36 mm eller större metalhuvud hade en ökad risk för omoperation vid långtidsuppföljning. Teorin bakom inferioriteten av 36 mm eller större metalhuvud omfattar plastslitage, korrosion i förbindelsen mellan protesstammen och ledhuvudet samt ökat friktionsmoment som överförs till cupens yta och kan äventyra cupfixationen.

Studierna i denna avhandling syftar i att förbättra vår kunskap om fördelar och nackdelar med användandet av större ledhuvud vid total höftledsplastik.

För att utvärdera om ökning av ledhuvud från 28 mm till 32 mm och därefter till 36 mm har minskat risken för luxation, studerades 186,231 patienter i en gemensam registerdatabas som omfattar dem danska, finska, norska, och svenska höftprotesregistren (**studie I**). Resultaten visade att patienter som fick en höftprotes på grund av artros och hade opererats med ett 32 mm ledhuvud hade mindre risk för omoperation på grund av luxation jämfört med patienter som fick ett 28 mm ledhuvud. Patienter som hade opererats med 36 mm ledhuvud hade samma risk för omoperation på grund av luxation men större risk för omoperation på grund av lossning jämfört med patienter opererade med ett 32 mm ledhuvud. Det är oklart om detta beror på sämre egenskaper av höftplastik med 36 mm ledhuvud eller om det kan handla om en selektion av patienter med riskfaktorer för luxation i grupper med större ledhuvud.

Patienter som får en höftprotes på grund av höftfraktur löper ännu högre risk för luxation jämfört med artrospatienter. Därför har effekten av ledhuvudstorlek studerats separat hos denna patientpopulation (**studie II**). Databasen beskriven ovan användes för att identifiera 2515 patienter som fått en höftprotes efter höftfraktur med ett 36 mm ledhuvud. Dessa patienter matchades med 2515 patienter som fått ett 32 mm ledhuvud, baserat på deras ålder, kön, operationssår, typ av snitt, protesfixation och artikulationsmaterial. Syftet med matchningen var att motverka obalansen av patientrelaterade och kirurgtekniska riskfaktorer för luxation mellan olika ledhuvudstorlekar. Studien visade ingen skillnad i risken för omoperation på grund av luxation mellan grupperna opererade med 32 och 36 mm ledhuvud.

För att utvärdera om användandet av större ledhuvud påverkar plastslitage randomiserades 96 patienter till att få antigen det största möjliga ledhuvudet (36-44 mm) eller ett 32 mm ledhuvud (**studie III**). Samtliga patienter opererades med ett metalledhuvud och ett vitamin E dopad korslänkad plast. Vid tvåårsuppföljning påvisades ingen skillnad i plastslitage mätt med röntgen stereofotogrammetri (RSA).

Kobolt, krom och titanjoner i blodet anses vara tillförlitliga markörer för konkorrosion. För att utvärdera om användandet av större metalhuvud är förenad med större risk för att utveckla konkorrosion jämfördes metaljoner mellan patienter som fick det största möjliga ledhuvudet (36-44 mm) och patienter som fick ett 32 mm ledhuvud (**studie IV**). Vid ett- och två-årsuppföljning var halterna av metaljoner väldigt låga och skilde sig inte mellan grupperna.

I **studie V** utvärderades huruvida de ökade friktionsmoment som uppstår vid 36 mm eller större metall-plastartikulationer kan påverka cupfixation. Patienter som erhöll en ocementerad höftprotes randomiserades till antigen det största möjliga ledhuvudet (36-44 mm) eller ett 32 mm ledhuvud. Vid tvåårsuppföljning mätes cupmigration med hjälp av RSA. RSA är en noggrann röntgenmetod och tidig migration mätt med RSA kan prediktera risken för senare aseptisk lossning. Det fanns inga skillnader i migration mellan grupperna.

Sammanfattningsvis har avhandlingen visat att 32 mm ledhuvud minskar risken för luxation jämfört med 28 mm. Användningen av 36 mm ledhuvud i de nordiska länderna förefaller inte minska risken ytterligare. Det kan spekuleras att större huvuden än 36 mm behövs för att minska risken för luxation. Användning av större ledhuvuden kan hypotetiskt innebära andra nackdelar. Avhandlingens visade att användande av ännu större ledhuvud än 36 mm orsakar inte ökat plastslitage, korrosion eller påverkar cupfixation. Med tanke på den relativt korta uppföljningstiden behövs det studier med längre uppföljning för att verifiera avhandlingens resultat avseende risker vid användning av större ledhuvuden än 36 mm.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Tsikandylakis G, Karrholm J, Hailer NP, Eskelinen A, Makela KT, Hallan G, Furnes ON, Pedersen AB, Overgaard S, Mohaddes M. No Increase in Survival for 36-mm versus 32-mm Femoral Heads in Metal-on-polyethylene THA: A Registry Study. *Clin Orthop Relat Res*. 2018 Dec;476(12): 2367-78.

II. Tsikandylakis G, Karrholm J. N, Hallan G, Furnes O, Eskelinen A, Makela K, Pedersen AB, Overgaard S, Mohaddes M. (2020). Is there a reduction in risk of revision when 36-mm heads instead of 32 mm are used in total hip arthroplasty for patients with proximal femur fractures? *Acta Orthop* 91(4): 401-407.

III. Tsikandylakis G, Mortensen KRL, Gromov K, Mohaddes M, Malchau H, Troelsen A. Does the use of the largest possible metal head increase the wear of vitamin E-doped cross-linked polyethylene? Two-year results from a randomized controlled trial. *Submitted manuscript.*

IV. Bunyoz K, Tsikandylakis G, Mortensen KRL, Gromov K, Mohaddes M, Malchau H, Troelsen A. No difference in whole blood metal ions for 32 mm versus 36-44 mm femoral heads in metal-on-polyethylene Total Hip Arthroplasty: A 2-year report from a randomized control trial. *Submitted manuscript.*

V. Tsikandylakis G, Mortensen KRL, Gromov K, Troelsen A, Malchau H, Mohaddes M. The Use of Porous Titanium Coating and the Largest Possible Head Do Not Affect Early Cup Fixation: A 2-Year Report from a Randomized Controlled Trial. *JB JS Open Access. 2020;5(4):e20.0010*

CONTENTS

ABBREVIATIONS

ASA	American Society of Anaesthesiologists
CoC	Ceramic on Ceramic
CoP	Ceramic on Polyethylene
UHMWPE	Non cross-linked Ultra High Molecular Weight Polyethylene
DMC	Dual Mobility Cup
HHS	Harris Hip Score
HR	Hazard Ratio
MoM	Metal on Metal
MoP	Metal on Polyethylene (regardless the type of polyethylene)
MoXLPE	Metal on highly cross-linked polyethylene
MoVEPE	Metal on vitamin E doped highly cross-linked polyethylene
NARA	Nordic Arthroplasty Register Association
OHS	Oxford Hip Score
RCT	Randomized Controlled Trial
RSA	Roentgen Stereophotogrammetric Analysis
SHAR	Swedish Hip Arthroplasty Register
THA	Total Hip Arthroplasty
UCLA	University of California Level of Activity rank score
VEPE	Vitamin E doped highly x-linked Polyethylene
XLPE	Highly X-Linked Polyethylene (non-containing vitamin E)

DEFINITIONS IN SHORT

Bearing	An articulating surface comprising a cup and a femoral head regardless the material the components are made of.
Condition number (CN)	A number used in RSA that describes the scattering of the marker beads in the bone. A low CN denote good scattering. In Sweden, CNs below 150 are recommended. CNs of 100-110 are considered very reliable for the detection of implant migration [143].
Hypomochlion	Fulcrum. The point of impingement causing the femoral head to translate instead of rotating.
Large heads	Femoral heads or bearings with a diameter of 36 mm or bigger.
Mean error of rigid body fitting	A number used in RSA that describes the stability of the marker beads within a rigid body. In Sweden, an upper limit of mean error of rigid body fitting of 0.35 is recommended [143].

1. INTRODUCTION

The close to-excellent results of total hip arthroplasty (THA) and the improvement in health-related quality of life and activity level that it provides have made it to one of the most cost-effective surgical procedures [86]. Most patients undergoing a THA at the age of around 70 will probably not need any reoperation, as the 10-year survival of the primary hip prosthesis exceeds 95 % for the usual THA candidate [127]. In spite of this, the definition of "common" patient is continuously changing, as THA is offered to even younger patients with even greater requirements and expectations of hip function, in whom THA may fail sooner than expected [103]. Apart from periprosthetic infections that could occur in any patient and at any time, the 2 main reasons for THA failure are instability, leading to recurrent dislocations, and wear-related implant loosening, both associated with the size of the prosthetic femoral head, among other patient- and implant-specific factors. This thesis focuses on the impact of head size on the stability of THA, wear between the articulating and modular components of the hip prosthesis and cup fixation.

1.1. FROM ORTHOPEDIC HISTORY TO CONTEMPORARY TOTAL HIP ARTHROPLASTY

When the modern THA was introduced in the 1960s by John Charnley, he used a 22.225-mm, non-modular metal head in a cemented stem articulating with a cemented socket made of conventional, non-highly cross-linked polyethylene (UHMWPE) (Figure 1). The concept was called "low-friction THA" and aimed at minimizing the contact surface between the femoral head and the plastic socket, as well as enabling the use of a thick socket with enough polyethylene material to be worn as a function of use in the years to come. Since then, technical evolutions have resulted in more wear-resistant bearing materials, such as cross-linked polyethylene (XLPE), vitamin E-infused cross-linked polyethylene (VEPE) and ceramics. Apart from the traditional metal on polyethylene (MoP), different bearing combinations have been tested; they include ceramic on polyethylene (CoP), ceramic on ceramic (CoC) and metal on metal (MoM). Wear-resistant bearings have encouraged surgeons to use larger modular femoral heads in THA in order to reduce dislocation rates (for reasons explained further down), as the risk of wear became less worrisome. A gradual increase in bearing size occurred from 22 mm in the 1960s to 28 mm in the 1990s and then to 32 mm in the mid-2000s, according to various register reports [3, 6, 36, 45, 92, 107, 110]. Since then, the use of 36-mm heads has increased (Figure 2) and taken over from 32-mm heads in some countries such as Denmark [36] (Figure 3). Regarding the use of bearing materials, MoP bearings are used predominately in the Nordic countries [36, 107, 110, 127], while CoP bearings are more common in central Europe [45, 92] (Figure 4). As a result, 32- and 36-mm MoP or CoP bearings appear to be most common in THA. However, polyethylene wear in large bearings is still a concern, especially in younger and highly active patients. Additionally, large bearings may generate greater torques that could compromise the fixation of the cup or the junction between the modular head and the neck of the stem and cause fretting and corrosion.

Figure 1. *A: The Charnley prosthesis consisting of a monoblock cemented metal stem with a 22-mm head articulating with a cemented conventional polyethylene socket. B: A modern prosthesis consisting of an uncemented socket lined with a cross-linked polyethylene and articulating with a modular 32-mm head tapered on an uncemented stem coated with hydroxyapatite. Figure 1 is published with the permission of DePuy-Synthes.*

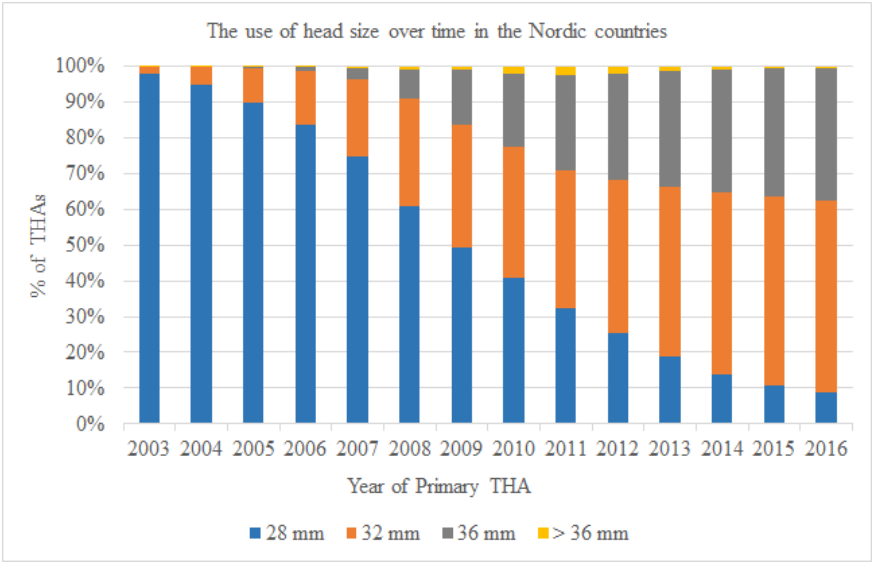


Figure 2. *The diameter of head size used in THA has increased; 32-mm heads continue to increase at the expense of 28-mm heads while 36-mm heads have also increased but not as rapidly as 32-mm heads. Data from the Nordic Arthroplasty Register Association.*

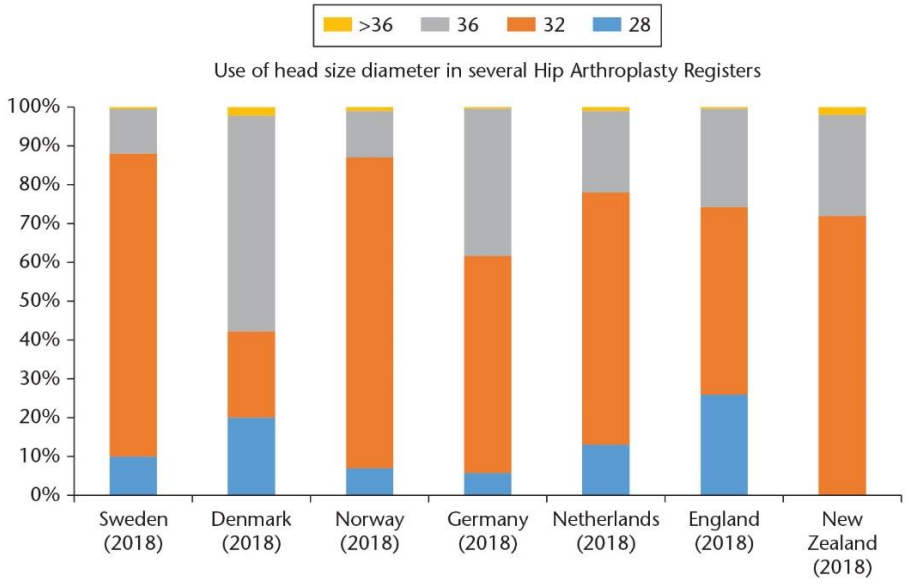


Figure 3. *According to the latest register reports, 32- and 36-mm heads are most common in contemporary THA. Published in EFORT Open Reviews 2020 [140].*

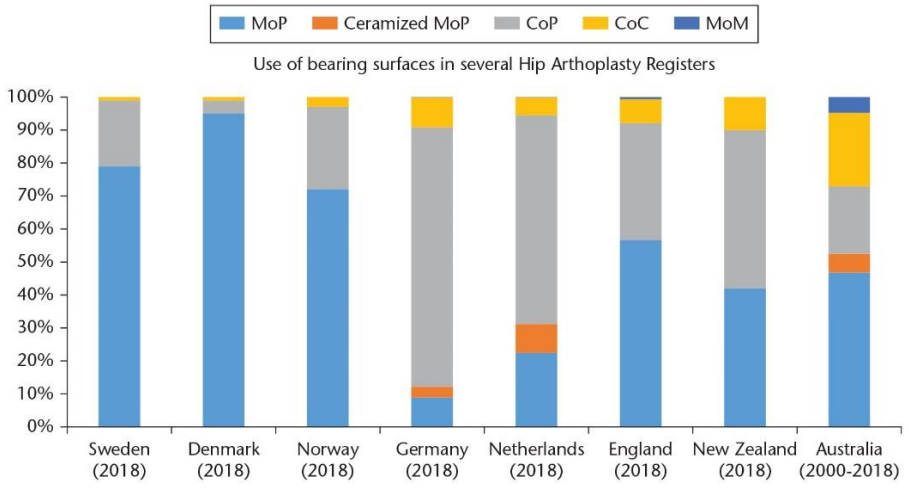


Figure 4. *Metal-on-polyethylene bearings are most common in the Nordic countries and England, while ceramic-on-polyethylene bearings are more popular in Central Europe. Published in EFORT Open Reviews 2020 [140].*

1.2. HEAD SIZE AND DISLOCATION

1.2.1. Pathophysiology of dislocation

In contrast to a native hip joint, a hip replacement functions as a true "ball and socket" joint. Apart from the congruency between the cup and the head and the tension provided by the joint capsule and the surrounding muscles, especially the abductors, there is nothing else holding the head within the cup. It is therefore easier for dislocation to occur, provided that there is a hypomochlion that transforms the rotation occurring in the prosthetic joint into translation and levers the head from the cup. The head then must travel a certain distance until it disengages the cup and dislocates. This hypomochlion occurs whenever the components of the prosthesis impinge either on each other or against the surrounding tissues during the physiologic range of hip motion. Impingement usually occurs between the neck of the stem and the cup, a so-called "implant-implant impingement" (Figure 5), or, alternatively, between the patient's own structures (patient-patient impingement) or between the patient and the implant (patient-implant impingement). Some examples of patient-patient and patient-implant impingement are the greater trochanter impinging on joint capsule interposition, a large protruding cup or the patient's acetabulum and osteophytes. Impingement typically occurs at the extremes of hip range of motion, such as the internal rotation of the flexed hip (e.g. while sitting down and moving sideways or tying shoes) and the external rotation of the extended hip (e.g. turning left while standing with the right foot fixed on the ground).
Dislocation is a painful experience for the patient and, in most cases, it necessitates admission and closed reduction under anaesthesia. It usually occurs early, within the first year after surgery, and, unless there is an obvious mechanical reason that will lead to recurrent dislocations, the THA usually becomes stable when the surrounding tissues have healed. The incidence of THA dislocation has varied in the literature over time and it is probably around 2-3% considering modern implants and surgical techniques [28]. In about 18-50% of these patients, dislocation will reoccur [48, 111] and necessitate revision arthroplasty, which is reflected in the somewhat lower revision rates due to dislocation that arthroplasty registers report, ranging between 0.5-1% [75, 153]. Recurrent dislocations are the second or third leading cause of THA failure in the Nordic countries according to register reports [36, 47, 107, 127].

1.2.2. Risk factors

THA dislocation is multifactorial. There is a plethora of patient- and surgery-related risk factors for dislocation. Some of them may be more important than others when looking at them individually, but, when they accumulate, the result is an unstable THA.

Patient-related risk factors

In highly morbid patients, the risk of THA dislocation has been reported to be twice as high [48]. The presence of neuromuscular disorders, such as Parkinson's disease, cerebral palsy and dementia, increases the risk by approximately 2-4 times [48, 54, 151], probably due to the reduction in muscle control and compliance in this patient group. A history of spinal deformity/fusion has also demonstrated a high impact on the risk of THA dislocation (2-3 times increased risk [13, 54]) that could be attributed to reduced spinopelvic motion predisposing to THA impingement [11]. Advanced age has also been associated with THA dislocation in various publications [28, 59], probably through its confounding effect on comorbidities and muscle weakness. Female sex has been found to be weakly associated with THA dislocation; however, this finding has been inconsistent in the literature and probably lacks clinical significance. The indication for THA could also predict the risk of dislocation. Primary osteoarthritis is the main indication for THA. Other hip conditions treated with THA include inflammatory arthritis, osteonecrosis, hip dysplasia and any other condition that leads to secondary osteoarthritis of the hip. THA on the indication of osteonecrosis and hip dysplasia has demonstrated an at least twice as high risk of dislocation [10, 59, 145] compared with primary osteoarthritis. Patients undergoing a THA for the treatment of a displaced femoral neck fracture deserve special attention when studying THA dislocation. Their advanced age, underlying morbidities and increased risk of falling puts them at a higher risk of THA dislocation that has been reported as being between 6-18% [14, 71, 113]. The higher mortality and morbidity burden [58] in these patients probably makes surgeons reluctant to revise them, which is reflected in the significantly lower revision rates due to dislocation (0.7-1.3%) reported in register studies [24, 70]. THA on the indication of femoral neck fracture puts patients at a 2-5 times higher risk of revision due to dislocation compared with THA after osteoarthritis, according to a Norwegian [17] and a Swedish [59] register study. This conclusion has been supported by several other studies worldwide [12, 24]. As the surgical technique evolves and our knowledge of treatment options for hip fractures increases, THA appears to be more beneficial than internal fixation or

hemiarthroplasty after displaced femoral neck fracture for the more active and lucid patient around or above pension age [121]. In 2016, there was a change in trend in Sweden, with more patients undergoing THA after a displaced femoral neck fracture, especially in the 55- to 64-year age group, indicating that most clinics are pushing down their lower age limit for THA. We are therefore anticipating an increase in life expectancy in patients with THA after a hip fracture that warrants the development of surgical techniques and implants that increase THA survival. Because of the high-risk profile for THA dislocation in patients with femoral neck fractures, the association between head dislocation should be studied separately from that of patients with hip osteoarthritis.

Surgery-related risk factors

Surgery-related risk factors, like implant placement and the restoration of hip anatomy, the method of implant fixation and surgical approach and, finally, the size of the prosthetic head, also play a significant role in THA stability. THA is a reconstructive procedure that aims to restore hip anatomy. This includes placing the cup in a way that follows the orientation of the native acetabulum, restoring the original center of motion, abductor lever arm and leg length. Back in 1978, Lewinnek et al. [88] described a safe zone for cup placement that comprised an inclination of 40°±10° and an anteversion of 15°±10°. Cups placed within the safe zone had demonstrated a dislocation rate of 1.5% as opposed to 6.1% for cups outside the safe zone. Putting the cup in the safe zone is apparently not an easy task, as even high-volume surgeons fail to accomplish it in up to 50 % of cases [19]. However, missing the safe zone does not necessarily lead to dislocation. Its "safety" has being questioned in more recent reports that have found the majority (58%) of dislocating THAs within Lewinnek's safety zone [4] and were unable to demonstrate any association between the inclination/anteversion of the cup and dislocation [134]. Restoring the hip center of motion is usually not an issue in routine cases of hip osteoarthritis, but it can be challenging in more severe cases such as dysplastic coxarthritis, where the hip center has moved cranially. Bringing down the hip center to match the healthy side could reduce the risk of THA dislocation. Using computer simulation, a more cranial placement of the cup reduced the impingement-free range of hip motion [74] and, in clinical settings, tripled the risk of dislocation for every 5 mm of cranialization [73]. Femoral offset is used as a measurable proxy to estimate the restoration of the abductor lever arm, as well as soft-tissue tensioning that helps keep the THA stable (Figure 6). Restoring the femoral offset has been reported as one of the most important factors in reducing dislocation rates [50] and increasing range of motion [69],

but its effect in reducing dislocation rates appears to lack consistency in the literature [30]. Cemented implant fixation has been highlighted as a preventive factor for dislocation [24, 102, 118], which is probably explained by a more precise and reproducible implant placement when cement is used. Among the surgical approaches used in THA, which could be summarized as direct anterior, lateral and posterior with their numerous modifications and eponyms, the posterior approach has consequently been associated with a higher risk of dislocation [59, 102, 153]. This is most probably due to the disruption of the posterior capsule and external rotators. In hip osteoarthritis, internal rotation becomes stiff due to the contracture of the posterior capsule. This contraction prevents the hip from coming to extreme flexion and internal rotation, which is the usual mechanism of posterior dislocation. Through a posterior approach, the posterior capsule and external rotators are dissected, making this approach less forgiving in terms of component malpositioning and failure to restore hip anatomy and thereby more susceptible to dislocation, especially when these posterior structures are left unrepaired [48]. Increased awareness of the challenges of the posterior approach may be a possible explanation of contemporary THA through a posterior approach having the same risk of revision due to dislocation as THA through a lateral approach, as reported in a recent study [132]. Finally, identifying and eliminating impingement caused by osteophytes and excessive joint capsule during surgery is crucial for the prevention of dislocation. Head size has a decisive impact on dislocation through two main mechanisms; altering the impingement-free range of motion and the jumping distance.

Figure 5. *A: Impingement occurring between the neck of the stem and the rim of the cup (red circle). B: Evidence of impingement with the neck leaving its footprint on the cup (red circle). Picture owned by the author.*

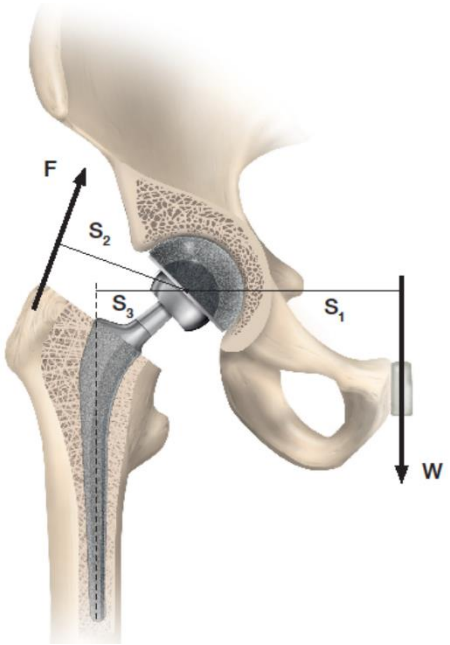


Figure 6. *The torque created by the patient's weight (W) and its lever arm (S_1) needs to be balanced by the torque created by the abductor pull (F) and its lever arm (S_2). The greater the abductor lever arm, the greater the tension in the soft tissues surrounding the prosthetic hip, which increases its stability. Femoral offset (S_3) is the projection of the hip center on the longitudinal axis of the stem. The greater the femoral offset, the greater the abductor lever arm .*

1.2.3. Head size and impingement-free range of hip motion

There is a common belief among orthopedic surgeons, supported by several publications cited below, that larger heads reduce the risk of THA dislocation, as they allow a wider range of impingement-free hip motion. This is probably the main reason driving the increase in head size over time. There might be other causes that affect the range of motion of a prosthetic hip, such as obesity, preoperative range of motion, surgical approach, extent of soft-tissue release, implant design and implant positioning. However, head size is an independent factor with a strong impact on the range of motion. Finite element analysis has shown an increase in hip range of motion by 28% or 30°, as head size increased from 22 mm to 40 mm given a constant neck thickness, i.e. as the head-neck ratio increased [27] without taking the surrounding tissues in consideration. Increasing the head–neck ratio enabled a wider range of motion before the neck of the stem impinged on the cup (Figure 7). However when the surrounding tissues were considered, increasing the head diameter to above 38 mm did not lead to any further increase in range of motion, because implant-to-implant impingement had already been eliminated [15]. Instead, hip movement was limited by bone-to-bone or bone-to-implant impingement. In order to overcome the latter, other measures, such as increasing the femoral offset [69] or changing the femoral anteversion, are required [15]. Clinical studies measuring either the intraoperative [141] or postoperative [97] range of motion have confirmed the positive effect of larger heads on the impingement-free range of hip motion, especially in flexion, abduction and internal rotation. These studies have, however, compared either smaller than modern head sizes (e.g. 26 mm vs 32 mm) or non-adjacent sizes (e.g. 28 mm vs 40 mm). When 36-mm heads were compared with even larger ones (40 mm-54 mm), no difference in hip range of motion was observed [35], which confirmed that implant-to-implant impingement is completely eliminated with head sizes of 36 mm or more.

1.2.4. Head size and jumping distance

At some point in the internal rotation of the flexed hip or external rotation of the extended hip, impingement will eventually occur between the patient's own anatomic structures, even with a large head. However, a larger head could still enhance THA stability by providing a greater jumping distance. The latter is defined as the lateral translation that the head needs to travel before dislocating (Figure 8). Sariali et al. investigated the implant characteristics that affect jumping distance and found that an increase in head size of 1 mm resulted in

an increase in jumping distance of 0.4 mm [123]. However, jumping distance was also dependent on cup inclination and anteversion, as well as head offset (Table 1). For example, an increase in head diameter from 32 mm to 36 mm is expected to increase the jumping distance by 1.6 mm but only if the cup is placed at the correct inclination angle of 45°. If the cup is placed at a steeper angle of 55° or more, no gain or even a decrease in jumping distance may occur (Figure 8). The increase in jumping distance could probably explain why larger heads (ranging from 28 mm to 44 mm) required greater torques and a more extreme range of internal rotation of the flexed hip in order to dislocate in a cadaver study that compared head diameters of 28, 32, 36, 40 and 44 mm [37]. The difference in internal rotation needed for dislocation was, however, not significant for adjacent head sizes. So, should impingement occur, larger head sizes appear to provide THA with a safer margin before dislocation occurs, through a greater jumping distance, provided that there is an optimal cup orientation.

Table 1. The effect of head size, cup inclination, cup anteversion and caput offset on jumping distance.

	Increase of jumping distance	**Cup inclination**	**Head size**
Head size	0.40 mm/mm	45 grades	
	0.25 mm/mm	60 grades	
Cup inclination	-0.25 mm/grade		32 mm
Cup anteversion	0.05 mm/grade		32 mm
Caput offset	-0.92 mm/mm		

Data extracted from the original publication of Sariali et al. [123]

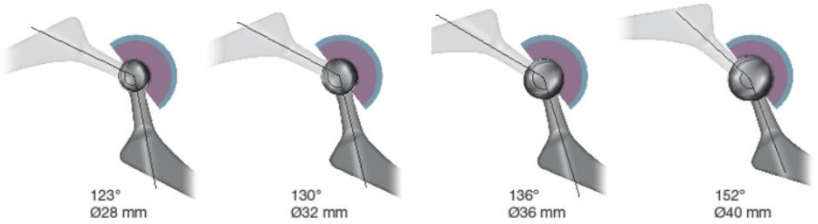


Figure 7. *By using a larger head while keeping the neck thickness constant (increasing the head-neck ratio), a wider range of motion is allowed before the neck impinges on the cup (implant-to-implant impingement).*

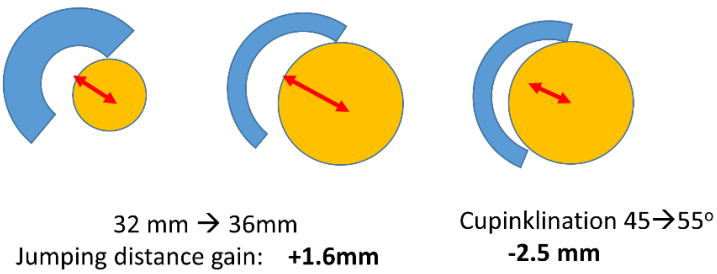


Figure 8. *Jumping distance (red arrow) is the horizontal distance that the head needs to travel before disengaging from the cup. Increasing the head size from 32 to 36 mm will increase the jumping distance by 1.6 mm but only if cup abduction remains constant. If the cup is placed at 10° more abduction, the gain in jumping distance from using a larger head is lost.*

1.2.5. Bipolar femoral heads in dual mobility cups

Since larger femoral heads provide a greater jumping distance, it is easy to speculate that using the largest possible head could substantially reduce or possibly eliminate the risk of dislocation. However, in MoP bearings, the most common bearings used worldwide, head diameter is limited by the size of the native acetabulum and subsequently the size of the cup that can be inserted, in order to maintain a minimum polyethylene thickness. In numbers, the largest possible head that can be inserted, in contemporary MoP THA, ranges from 28 mm in small patients with a small acetabulum up to approximately 40 mm in tall patients. If even larger heads are to be used, then other bearing materials such as CoC and MoM need to be chosen. MoM THA and hip resurfacings allow for the insertion of femoral heads that are as large as the native femoral head. These head diameters are referred to as anatomic. The dual mobility cup (DMC) is a variation of MoP THA. The DMC concept introduces a second bearing surface between a thin metal shell and a "mobile polyethylene insert", which is in practice a polyethylene head that determines the effective head size (Figure 9). The latter accommodates a smaller (initially 22 and more recently 28 mm) modular metal head in a constrained fashion and together builds a bipolar head, the diameter of which is almost as large as the native femoral head and may range from 44 to 56 mm or even more, depending on the patient's size. As a result, the bipolar heads used in DMCs provide THA with a considerably larger jumping distance and are expected to reduce dislocation rates. Originally a French invention from the 1970s, DMCs have not met with widespread recognition, although the reported dislocation rates have been as low as 0.46% after primary THA [29]. This is probably due to implant-specific complications such as intraprosthetic dislocation and aseptic loosening related to older versions of the DMC concept that used non cross-linked polyethylene and a 22-mm inner head. Intraprosthetic dislocation is the separation of the inner metallic head from the outer plastic head, the incidence of which had been reported as 3.3%, but no intraprosthetic dislocations have been reported after 2007 [29]. There were also concerns about increased polyethylene wear and subsequent aseptic loosening due to the double MoP articulation. However, the rates of aseptic loosening have been reported to be comparable with those of single-mobility cups (1.3%) [29]. Modern DMCs with a 28-mm inner head and a XLPE outer head could therefore be a viable alternative to single-mobility cups, but there are still no randomized, controlled trials that support this statement.

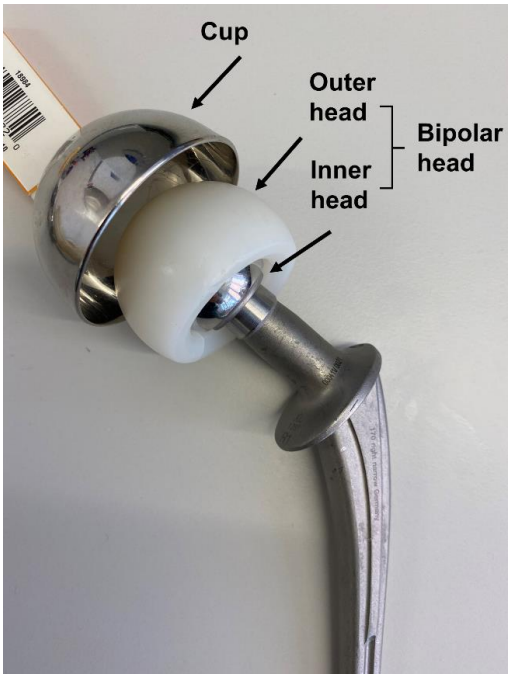


Figure 9. *Illustration of a bipolar head in a dual mobility cup construct. The construct consists of a metal cup that is fixed in the acetabulum and a bipolar head. The bipolar head consists of an outer plastic head made of cross-linked polyethylene, which is as large as the inner diameter of the cup and approximates the diameter of the biological femoral head. The outer head accommodates a 28-mm modular metal head, which is connected to the stem in a standard taper fashion. The effective head size is determined by the size of the outer head that also provides the benefits of impingement-free range of motion and jumping distance. Picture owned by the author.*

1.2.6. Head size and THA dislocation in clinical studies

Several studies have supported the hypothesis that the use of larger head sizes results in lower dislocation rates. In a study of 51,901 patients in the USA, dislocation rates dropped from 4% to 2% between 1997 and 2005 and plateaued until the end of the observation period (2011), while the use of 32-mm or larger heads increased from 10% to 80% [56]. Accordingly, a decreasing trend in dislocation rates has been observed in the National Health Service, as the use of heads smaller than 36 mm also decreased between 2004 and 2010 [68]. There are a few randomized, controlled trials (RCT) investigating the effect of head size on THA dislocation. Howie et al. [65] reported a decrease in dislocation rates from 4.4% to 0.8 when 36-mm heads were used instead of 28 mm. In another RCT, Lee et al. [87] compared 28-mm with 32-mm heads and reported no difference in dislocation rates, but the study was underpowered. Nevertheless, 28-mm heads are barely used in contemporary THA. A third RCT performed on revision THA, where the risk of dislocation is generally increased, reports a decrease in risk from 8.7% to 1.1% when 36-mm or 40-mm heads were used compared with 32 mm [53]. Given the low frequency of dislocation in modern THA, it is difficult to

perform a sufficiently powered RCT to investigate a potential difference in dislocation rates between head sizes. If a decrease in dislocation rates from 2% to 1% is considered clinically meaningful, a sample size of over 4,600 patients would be required (2-sided z-test for comparison of proportions). Register studies are an alternative method of studying the role of head size, as they provide much larger sample sizes with almost self-evident statistical power that allows for the detection of small effect sizes. However, they have their own limitations due to the lack of randomization and inability to adjust for unmeasured confounding. Additionally, the outcome in register studies is revision due to dislocation, because dislocations treated with closed reduction are not usually registered. In the Norwegian Arthroplasty Register, 32-mm heads were compared with 28-mm and 22-mm in 42,987 patients and an increased risk of dislocation was found when heads smaller than 32 mm were used [17]. In the Swedish Hip Arthroplasty Register (SHAR), 28-mm heads were compared with 22-, 32-, 36-mm and bipolar heads in DMCs in 78,098 patients. The 22-mm heads entailed twice the risk of dislocation compared with 28-mm heads, but no statistically significant differences were found for 32- and 36-mm heads [59]. The Finnish Arthroplasty Register compared 28-mm heads with 32-, 36- and > 36-mm heads in a case mix of bearing materials in 42,379 patients and reported risk ratios of around 0.4 for 32- and 36-mm heads and even lower (0.09) for > 36 mm [75]. Equally low hazard ratios (HR) for dislocations were reported when bipolar heads in DMCs were compared with 28- to 36-mm heads in a propensity matched study of 2,227 patients from the Nordic Arthroplasty Register Association database [77]. In the Kaiser Permanente Total Joint Replacement Registry, analysing data from 19,623 surgeries, the use of heads smaller than 32 mm entailed an increased risk of revision due to dislocation compared with 36-mm heads (HR 3-15 depending on the head material) [18]. The abovementioned register studies either used a 28-mm head as the reference or have compared 32-mm or 36-mm heads with a case mix of heads smaller than 32 mm. They are therefore unable to provide any evidence on whether the use of heads larger than 32 mm reduces the risk of dislocation compared with 32 mm, which appears to be the contemporary standard. The only register study that used 32-mm heads as the reference and compared them with larger heads, comes from the Dutch Arthroplasty Register (N=166,231), showing an HR of 0.63 for 36-mm heads, but, after stratifying for surgical approach, this difference was only statistically significant for the posterior approach [153]. Moreover, all the abovementioned studies have been performed on patients with either osteoarthritis or a case mix of hip diagnoses. There are only 3 register studies that have investigated the effect of head size on dislocation specifically in patients with a femoral neck fracture. The first is from the Lithuanian Arthroplasty Register that compared 28-mm with 32-mm heads in 1,412 patients and found no difference between them [22]. The second

is from the National Joint Registry (UK), performed on 4,323 patients and comparing 28-mm heads with both smaller and larger heads (as one group), without finding any difference between them [67]. Only when head size became large enough to approximate the anatomic head diameter, was there any significant reduction in the risk of revision due to dislocation, as shown in a study from the Nordic Arthroplasty Register Association database that compared bipolar heads in DMCs (HR 0.45) with 32- to 36-mm THA in 9,040 patients with a proximal femur fracture [70]. In spite of this, the question of whether a head larger than 32 mm in contemporary MoP THA after a femoral neck fracture could reduce the risk of dislocation remains unanswered.

1.2.7. The Nordic Arthroplasty Register Association (NARA)

As stated above, the use of register databases could produce studies with sufficient power to study the effect of head size on dislocation. However, given the low incidence of revision due to dislocation, even large national databases such as the SHAR could fail to deliver sufficiently large sample sizes, especially after selection criteria and/or matching processes have been applied. In these cases, an initial sample size of hundreds of thousands of patients could easily fall to a few thousand. In order to study rare events, national arthroplasty registers need to join forces and merge into larger databases. The NARA is a collaboration between the national arthroplasty registers of Denmark, Finland, Norway and Sweden. It was initiated in 2007, including Denmark, Norway and Sweden, while Finland joined in 2010. It is an integrated database that includes 25 variables for hip arthroplasty. However, only variables that are registered in all four national registers can be merged, making the NARA a less detailed database than the national registers. Due to the unique personal identification number that all 4 countries apply, patients can usually be followed after an index operation until revision, death or emigration. Almost all hospitals, public and private, report their THAs to their respective national arthroplasty register, which makes the coverage of the NARA database approximately 100%. The easy linkage between each national arthroplasty register and national patient register allows for vigorous validation studies and helps keep the completeness of each national arthroplasty register at very high levels. For primary THA, the completeness is 95-98% and, for revision THA, 80-95%, according to the latest annual reports from each national arthroplasty register [36, 47, 107, 127]. The NARA includes more than 700,000 THAs registered since 1995 and has led to several publications that have influenced orthopedic practice, such as the

abandonment of MoM bearings and uncemented fixation in the elderly in the Nordic countries [95].

1.3. ASPECTS OF POLYETHYLENE WEAR AND CORROSION

1.3.1. The evolution of polyethylene in THA

In MoP THA, the weakest link that may cause failure is the polyethylene cup or insert. As a function of use, polyethylene wears and releases small particles that may cause a foreign body reaction, macrophage-induced osteoclast activation and periprosthetic osteolysis with subsequent prosthesis loosening and failure [149]. By increasing the head diameter, the contact area between the head and the cup increases, raising concerns about increased polyethylene wear. The use of larger heads in THA would not have been possible without technological advances in the manufacture of more wear-resistant polyethylene. When low-friction arthroplasty was introduced in the 1960s, John Charnley used ultra-high molecular weight polyethylene (UHMWPE), which was sterilized with low-dose irradiation (2.5-4 Mrad) and produced some linkage between the polyethylene chains. He reported an average annual wear rate of 0.15 mm, 0.18 mm/year during the first 5 years and 0.10 mm/year during 5-10 years with a 22-mm head [23]. It took almost three decades of refining polyethylene materials before the breakthrough came in the late 1990s: highly cross-linked polyethylene (XLPE). The latter is processed with higher doses of irradiation (5-10 Mrad) in order to achieve maximum cross-linking and therefore wear resistance. The downside of this process is the production of free radicals that interact with oxygen and lead to oxidation, which over time reduces the mechanical properties of the polymer. To address this issue, XLPE is either remelted, which completely removes free radicals but also reduces cross-linking, or heated just below its melting point (annealing), which removes some of the free radicals but preserves cross-linking [131]. XLPE has demonstrated 50% lower wear rates ($\leq$ 0.05 mm/year), a lower incidence of osteolyses and lower revision rates [38, 43, 117, 131] and has therefore gradually replaced conventional UHMWPE. There are, however, some concerns about the increased bioactivity of the smaller

particles released from XLPE that could lead to a more intense foreign body reaction [42], but these concerns are not supported by the clinical outcomes of XLPE. Further developments of XLPE have aimed to neutralize the free radicals produced by irradiation without compromising cross-linking. The second generation of XLPE comprises three polyethylenes produced using three different methods. The first is sequentially irradiated and annealed with lower doses (3 Mrad) in three cycles, resulting in a total dose of 9 Mrad. The second is irradiated with 5 Mrad, followed by compression (mechanical annealing) and reheating. The third, which is the one used in subprojects III-IV in this thesis, is irradiated at a maximum of 10 Mrad and then soaked in liquid vitamin E at an elevated temperature below the melting point, to allow homogenization, which binds the free radicals. This method theoretically provides greater oxidation resistance without compromising wear resistance, as the polyethylene does not need to be remelted or annealed [131]. The latter is usually referred to as vitamin E-diffused polyethylene (VEPE) and has demonstrated wear rates equal to those of other second-generation XPLE when ceramic heads were used up to 7 years of follow-up [52, 108]. However, when metal heads are used, after initially equal wear rates at 2 years [128], VEPE has demonstrated lower wear rates during the period of 2-5 years compared with other second-generation XLPE [51].

1.3.2. Methods for measuring polyethylene wear

Polyethylene wear is the amount of polyethylene debris produced by adhesion or abrasion when the femoral head moves in the cup. The optimal measurement would be to weigh the polyethylene before and after it has been used. The difference in weight expressed in mg would be a very accurate estimate of wear. However, this is not possible in clinical trials. For this reason, radiologic studies are used in order to estimate the volume of debris, which is referred to as "volumetric wear" expressed in mm^3. As polyethylene wears, the femoral head penetrates into the cup and removes a cylinder of polyethylene, the volume of which can be calculated using the formula:

$$Volumetric\ wear = head\ penetration\ \pi\left(\frac{head\ \ diameter}{2}\right)^2$$

If the same head diameter is used, head penetration expressed in mm has a linear relationship with volumetric wear and could therefore be used as a proxy to compare wear between different bearing materials [16]. Head penetration is usually referred to in studies as the "linear wear". Most studies investigating

polyethylene wear refer to a threshold of 0.1 mm/year for the prediction of wear-related complications. This threshold probably originates from John Charnley's reports [23] and applies to conventional UHMWPE and small (22-28 mm) head sizes, which corresponds to a volumetric wear of 40-60 mm^3/year. In another study also referring to conventional UHMWPE, the total volume of wear required for osteolyses to occur has been estimated at 670 mm^3 [41], which theoretically gives a traditional 22- or 28-mm UHMWPE THA an osteolysis-free life span of 17 or 11 years respectively. For comparison, in modern 32- or 36-mm XLPE THA with linear wear rates of less than or equal to 0.05 mm/year, the corresponding volumetric wear could be up to 40-51 mm^3/year. It thus appears that the benefits in wear resistance gained by the use of XLPE instead of UHMWPE could theoretically be neutralized by the use of larger heads in terms of volumetric wear. However, the thresholds of wear rates for UHMWPE cannot be generalized for XLPE. To date, there are no known thresholds for total or annual volumetric wear of XLPE associated with the presence of clinically relevant osteolyses. Head penetration is usually assessed with roentgen-stereophotogrammetric analysis (RSA). It has been observed that head penetration rates increase during the first couple of postoperative years, and have been reported as up to 0.03-0.05 mm/year for contemporary XLPE [128]. This initial phase is referred to as the "bedding-in" period and is attributed to the plastic deformation of the polyethylene and/or further advancement of the polyethylene press-fit into the cup rather than actual polyethylene wear. The reported head penetration rates then decrease to as little as 0.02 mm/year [51] and are attributed to the actual polyethylene wear, also referred to as "steady-state wear".

1.3.3. Head size and polyethylene wear

The introduction of XLPE coincided with and probably encouraged the use of larger heads in THA. During the 1990s, 28-mm heads were regarded as a good balance between UHMWPE wear and stability [91]. In the 2000s, 32-mm and subsequently 36-mm heads combined with XLPE gradually replaced 28 mm. Using a hip simulator and gravimetric methodology, wear rates were found to be independent of head size up to 46 mm (22-46 mm) in MoXLPE bearings [106]. In clinical studies, there is some controversy about whether large heads increase wear in modern polyethylene cups. Using a computer-assisted vector wear technique, "the Martell method" [96], higher volumetric wear rates have been reported for 36- and 40-mm heads (26 mm^3/year) compared with 32 mm (13 mm^3/year), although their linear wear rates did not differ at 10- to 14-year follow-ups [83]. When comparing 36 mm specifically with 40 mm in MoXLPE

bearings, no difference in linear or volumetric wear and no cases of aseptic loosening have been reported in a series of 107 hips at a mean follow-up of 8 years [82]. Other studies have used RSA to measure head penetration. In an RCT comparing 28-mm with 36-mm MoXLPE bearings, linear wear rates did not differ (0.01 and 0.00 mm/year) between 1 and 3 years postoperatively, but volumetric wear was not reported [64]. Callary et al. reported linear wear rates below 0.02 mm/year in 21 cases of 32-mm MoXLPE bearings with a 5-year follow-up [21]. They then followed 15 patients with 36- to 40-mm MoXLPE for 5 years and reported steady-state linear wear rates equal to those of 32-mm bearings [20], even if volumetric wear was not reported. The above studies indicate that it is almost impossible to measure steady-state linear wear differences with XLPE, even when head sizes above the contemporary 32 mm are used. However, volumetric wear increased when 36-mm or larger heads were used, but it has not been possible to establish any association between head size and wear-related complications, such as aseptic loosening. The longest mean follow-up in available prospective studies is 11 years [83]. On the other hand, register studies with longer follow-ups have raised concerns about the long-term effect of MoXLPE bearings larger than 32 mm on implant survival. The Australian Register has reported an increased risk of revision for any reason (HR 1.16) for > 32-mm heads compared with 32-mm heads [6]. Accordingly, the National Joint Registry has reported higher revision rates for 36-, 40- and 44-mm heads in MoP THA compared with 32 mm [110]. The increased revision rates could be associated with the increase in volumetric wear or other complications or could result from selection bias related to large heads, but this remains to be proven in long-term RCTs. Until then, most authors recommend the use of metal heads that are large enough to allow a minimum of 5-6 mm of XLPE thickness [55, 135] in order to avoid complete wear-through or fracture of the polyethylene. The combination of wear resistance, increased fatigue strength and antioxidant properties found in VEPE [114, 131] could make it suitable for the use of even larger heads in even thinner polyethylene inserts. There may be a benefit, in terms of wear, when VEPE is used instead of other second-generation XLPE combined with metal heads [51]. However, there are no clinical trials investigating the association between head size and wear in MoVEPE THA. One RCT has compared VEPE wear between 32-mm and 36-mm ceramic heads and found no difference in steady-state linear wear rates (0.02 and 0.01 mm/year respectively) up to 6 years [90].

1.3.4. Head size and corrosion

The use of modular heads has facilitated primary and revision hip surgery in terms of restoring hip anatomy and appropriately tensioning the hip joint, as the surgeon is able to choose between different head diameters, head material and neck extensions for the same stem. However, head modularity has introduced an additional interface that can, as a function of use, wear and corrode. Increased frictional torques in large bearings could be transmitted to the head-neck junction of the stem and cause micromovements that damage the interface between the head and the neck. This interface consists of a conical projection of the neck of the femoral stem, also called the trunnion, which is pressed in a corresponding machine engraving of the femoral head known as the taper (Figure 10). Corrosion is caused by the chemical environment, as metal is surrounded by joint fluid and electrolytes and can be accelerated by fretting wear caused by micromovements in the unlubricated surfaces between the trunnion and the taper (crevice corrosion), as well as by mixing different alloys (galvanic corrosion). The synergic effect of fretting with crevice corrosion is also known as mechanically assisted crevice corrosion (MACC) [112]. Corrosion is a natural process when metals interact with oxygen. In THA, corrosion may occur in any metal surface, such as the front or backside of the cup or the head or the stem, not only the taper-trunnion junction. Corrosion usually exerts a protective action on the inner layers of metal, but fretting damages this protective layer and exposes uncorded metal to the chemical environment of hip joint, which allows corrosion to penetrate deeper. Corrosion was initially observed in large MoM THA and was thought to be the result of fretting wear in the bearing surfaces. Not as frequent as in MoM THA, it has been observed in MoXLPE THA as well [81, 84] and can manifest with a variety of symptoms such as pain, swelling and limping. In MoXLPE THA, the only hard-on-hard interface that is susceptible to fretting and therefore corrosion is the taper–trunnion junction, provided that the cup and the stem are well fixed. Corrosion can lead to THA failure due to pain, the formation of pseudotumors in the hip, aseptic loosening [120, 148] and, in rare cases, even dissociation between the head and the neck [147]. Metal ions, such as cobalt, chromium and titanium, depending on the alloys used, are released in the periprosthetic tissues. Apart from adverse local tissue reactions and the formation of pseudotumors, metal ions can disseminate through the blood stream to many organs, such as the lungs, brain and kidneys, and reach concentrations similar to those in non-THA individuals with occupational exposure to metals [72]. This raises concerns about the potential systemic toxicity of metal ions, released from corroded metal surfaces, but they have not as yet been proven [76, 93, 150]. In retrieval studies with confirmed

trunnion/taper corrosion, blood cobalt and chromium ions have been found to be elevated, with cobalt ions increasing more than chromium ions [120, 148]. After THA revision, metal-ion levels decrease again [81] and are therefore regarded as a reliable marker for monitoring corrosion. Our knowledge relating to blood-ion levels originates from retrieval studies with already failed THA. There are therefore no globally accepted thresholds for metal-ion concentrations with a predictive value for THA complications related to corrosion. There are some national guidelines and recommendations for patients with MoM THAs that suggest that blood metal-ion levels of cobalt and chromium above 5 µg/L (Sweden) [2] or 7 µg/L (UK) [1] are indicative of closer follow-up and diagnostic imaging. However, in MoP bearings, lower mean blood-ion levels of 5.5 µg/L (0.9-10.5) for cobalt and 1.4 µg/L (0.5-4) for chromium have been reported in failed THAs due to corrosion-related complications [148]. Studies investigating the sensitivity and specificity of metal-ion levels for the prediction of corrosion-related complications suggest a cut-off value of 5 µg/L for cobalt or chromium in MoM bearings [60]. In MoP bearings, the suggested thresholds are even lower, at 1 µg/L for cobalt and a cobalt/chromium ratio of 1.4 to 2 [49, 79]. There are no suggested thresholds for titanium in MoP THA.

Risk factors for trunnion-taper corrosion

Trunnion corrosion is associated with several factors and head size is one of them. The theory behind this association is that larger heads create higher stress in the taper/trunnion interface. The greater frictional torque that large bearings generate could be transmitted to the head-neck junction and increase stress [116]. Another mechanism for increased stress is the increased horizontal distance between the head center and the center of the taper engagement area (Figure 11) [112]. Other factors associated with fretting corrosion include short roughened trunnion designs, mixing different alloys, increased stem offset, varus stem designs or varus stem placement, increased head length, low assembly forces, contaminated tapers, length of implantation, increased body weight and high-impact activities [46, 62, 104, 105, 115, 129, 136]. In vitro, the combination of titanium alloy stems with cobalt-chromium heads has been shown to be more susceptible to fretting and corrosion compared with the all cobalt-chromium head and stem, while the least susceptible combination was ceramic heads on cobalt-chromium stems [116]. In the same study, susceptibility to fretting and corrosion increased by reducing head length. The latter could be explained by the greater bending moments that are created when the head center is medialized in relation to the trunnion when head length is increased (Figure 12). Some retrieval studies have demonstrated a correlation

between head size and signs of fretting and/or corrosion in the taper-trunnion interface [33, 40] , while others have not confirmed it [129, 136]. As a result, there is some controversy about the association between head size and corrosion at the head-neck junction. The association between head size and blood-ion levels as an indicator of corrosion is less thoroughly investigated. In a case series of 60 THAs, metal ions were compared between 32-mm and 36-mm metal or ceramic heads coupled with XLPE. At a minimum 5-year follow-up, metal ions were undetectable in CoXLPE bearings, while, in MoXLPE, cobalt ions were detectable in 57% and chromium ions in 17% of patients. Of these, 36-mm heads had higher metal-ion concentrations than 32-mm heads [146]. To date, there are no RCTs investigating the relationship between head size and blood metal-ion levels in metal on cross-linked polyethylene bearings.

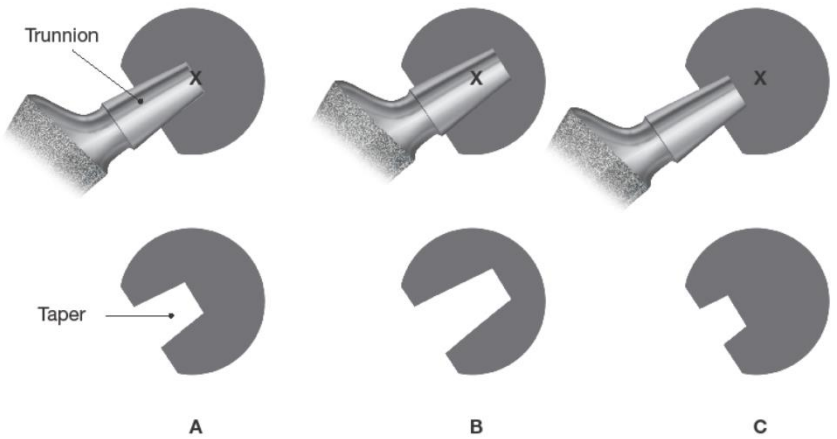


Figure 10. *A: Illustration of the trunnion and the taper for a head that has 0 mm head length. The depth of the taper is also known as the head bore. The head center (X) is at the tip of the trunnion. The head does not alter the offset of the stem. B: A head with -6 mm head length reduces the stem offset by moving the head center distally and laterally into the trunnion. The head bore and the contact area between the trunnion and the taper increase. C: A head with +6 mm head length increases the stem offset by moving the head center proximally and medially outside the trunnion. The head bore and the contact area between the trunnion and the taper decrease.*

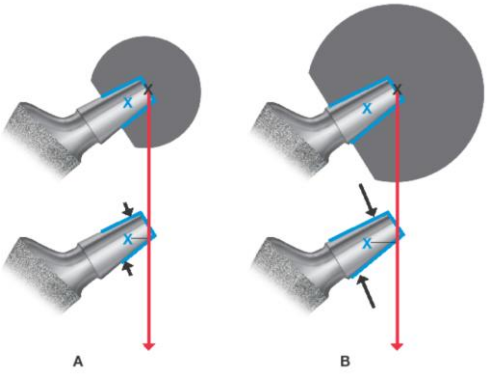


Figure 11. *The effect of head size on bending moments on the trunnion comparing 2 different head sizes of standard head length (+0 mm). A: The head center (black X) is at the tip of the trunnion. The load (red arrow) passes through the head center and creates a bending moment (black arrows) on the trunnion. The lever arm of the load is the projection (black line) of the center (blue X) of the taper engagement area (blue lines) on the vector of the load. B: An increase in head size increases the taper engagement area and lateralizes its center, thus causing an increase in the lever arm of the load increasing the bending forces acting on the trunnion.*

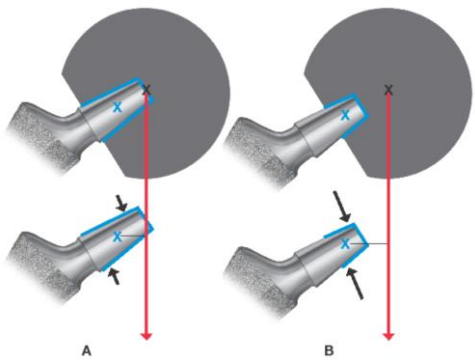


Figure 12. *The effect of head length on bending moments on the trunnion comparing 2 different head lengths with the same head diameter; +0 mm (A) and +6 mm (B). Increasing the head length medializes the head center (black X) but decreases the taper engagement area (blue lines). The center of the taper engagement area (blue X) is also medialized but to a smaller extent than the head center, resulting in a net gain in the lever arm of the load, thereby increasing bending moment and bending forces (black arrows) on the trunnion.*

1.4. HEAD SIZE AND FRICTIONAL TORQUE

Polyethylene wear and macrophage-induced foreign body reaction have been the predominant theory behind the presence of osteolysis and aseptic implant loosening. However, polyethylene wear fails to explain early and mid-term loosening, especially when modern wear-resistant polyethylene cups are used. RSA studies have shown that all hip implants migrate at an early stage postoperatively to a different extent and several thresholds of implant migration have been suggested for the prediction of future loosening. For cups, a 2-year proximal cup migration up to 0.2 mm is accepted because their 10-year survival exceeds 95% [119]. For stems, the thresholds differ depending on stem design and the type of fixation. For cemented, non-tapered polished stems, a 2-year subsidence of up to 0.15 mm [144] or up to 1.2 mm [80] is suggested as acceptable. A mean 2-year subsidence of 1.24 mm for cemented polished tapered stems and 0.40-0.66 mm for uncemented stems has been associated with > 97% 10-year implant survival [32]. These thresholds may be arbitrary and may not always succeed in predicting future loosening [133], but all the abovementioned studies have demonstrated that, the greater the early implant migration, the greater the risk of future loosening. Early implant loosening could be explained as the effect of inadequate primary implant fixation combined with increased mechanical stress at the bone-implant interface that maintains micromotion and accelerates the loosening process [101]. One of the factors that may increase mechanical stress at the bone-cup interface is the increase in frictional torques generated by large metal heads. As the head rotates within the cup, frictional torque is generated and is dependent on the joint reaction force, the head size and a coefficient of friction specific to the bearing material as follows [66] (Figure 13). In a laboratory study, comparing different bearing materials and head sizes, frictional torque was found to increase for 36- and 40-mm metal heads combined with XLPE compared with 32-mm heads [98]. If ceramic heads were used instead, frictional torque was independent of head size (28-36 mm). In the same study, VEPE compared with second-generation XLPE demonstrated higher frictional torques for both metal and ceramic 32-mm heads. For this reason, the combination of large metal heads with VEPE is expected to generate greater frictional torques. They could be transmitted to the bone/cup interface and compromise cup fixation. Rotational micromotions at the bone/cup interface have been reported to be greater for 32-mm MoP bearings compared with 32-mm CoC bearings [66]. A finite element analysis considering a saw-bone model with an implanted cemented MoXLPE THA found that an increase in head size from 28 mm to 32 mm and then 36 mm was associated with increased stress of up to 9% between the cement and the pelvic cortical bone [5]. Whether

the increased frictional torque and pelvic bone stress generated by larger head diameters, as shown in the abovementioned in-vitro studies, have any clinically relevant impact on cup fixation needs to be evaluated in clinical studies.

Figure 13. *The frictional torque generated at the bearing is a product of the joint reaction force (F), the head radius (R) and a coefficient of friction (μ) that depends on the bearing materials (Frictional torque = F R μ).*

2. KNOWLEDGE GAPS AND AIMS

Knowledge gaps

1. There are no available RCTs comparing dislocation rates between contemporary head sizes in THA. Due to the large samples required to demonstrate clinically meaningful differences in dislocation rates, it is unlikely that RCTs will ever reveal the optimal head size. The majority of register studies have been performed in a case mix of hip diagnoses with different risk profiles for dislocation. They have used 28-mm heads, which are regarded as historical in contemporary THA, as the reference. As a result, it is not clear whether the transition from 28 mm to 32 mm and mainly from 32 mm to 36 mm has led to a reduction in dislocation rates.

2. The association between head size and dislocation in patients with a femoral neck fracture is less well investigated. As it runs a considerably higher risk of dislocation, it is unclear whether this patient group could benefit from using 36-mm heads instead of 32-mm heads.

3. Technological evolution has produced considerably more wear-resistant polyethylene cups and inserts with second-generation XLPE and VEPE at their edge, which have encouraged surgeons to move from 22-mm or 28-mm heads to today's 32 mm or ≥ 36 mm. VEPE could theoretically enable the use of even thinner inserts. Despite in-vitro studies showing linear wear rates independent of head size, clinical studies have shown increased volumetric wear rates for ≥ 36-mm compared with ≤ 32-mm heads. Moreover, the combination of VEPE with larger metal heads could generate greater bearing friction that, along with inferior long-term register results for ≥ 36-mm heads, raises concerns related to these specific bearing sizes and materials. To date, there are no clinical studies investigating polyethylene wear related to head size in MoVEPE bearings.

4. Increased frictional torque in large MoVEPE bearings could also be transmitted distally and increase stress at the head-neck junction. Moreover, large heads increase stress due to their greater bending moments on the trunnion. Increased stress could accelerate MACC at the head-neck junction and release metal ions. The association

between head size and blood metal-ion levels is not thoroughly investigated. There are reports of metal-ion levels from retrieval studies of already failed THAs but there are no prospective studies comparing metal ion levels between different MoVEPE bearing sizes.

5. The increased frictional torque generated in large MoVEPE bearings could be transmitted proximally, to the pelvic bone-cup interface, and compromise cup fixation. No clinical studies have investigated whether large MoVEPE bearings could jeopardize cup fixation and lead to cup loosening.

Aims

The aim of this thesis is to:

1. Investigate whether there is a difference in the risk of revision and specifically due to dislocation between patients with hip osteoarthritis that have undergone surgery with 28-mm, 32-mm or 36-mm heads, using 32-mm heads as the reference.

2. Investigate whether there is a difference in the risk of revision and specifically due to dislocation in patients with a femoral neck fracture that have undergone surgery with 32-mm or 36-mm heads.

3. Investigate whether the use of the largest possible metal head in the thinnest possible VEPE insert increases polyethylene wear compared with a standard 32-mm head.

4. Investigate whether the use of the largest possible head in MoVEPE bearings could increase blood metal-ion levels compared with a standard 32-mm head.

5. Investigate whether the use of the largest possible head in MoVEPE bearings could jeopardize early cup fixation by increasing early cup migration compared with a standard 32-mm head.

3. PATIENTS AND METHODS

For the purpose of this thesis, 5 studies were conducted in 3 different patient samples. Studies I and II included 2 different patient samples from the NARA database. Studies III-V included the patients from a randomized, controlled trial entitled the "G7-RSA study".

3.1. STUDY I

Questions to be answered and hypothesis

A detailed summary of methods can be found in the corresponding publication [137]. In this study, the following questions were posed: 1) Is an increase in head size from 28 mm to 32 mm associated with a reduced risk of revision and specifically revision due to dislocation in patients undergoing THA on the indication of hip osteoarthritis? 2) Is a further increase from 32 mm to 36 mm associated with a further reduction in the risk of revision and revision due to dislocation? We hypothesized that increasing the head size would result in a reduced risk of revision due to dislocation.

Study design and patient selection

The study was designed as an observational, comparative, register-based study. Between 1995 and 2014, 662,943 THAs were registered in the NARA database. Patients undergoing surgery for the indication of primary hip osteoarthritis between 2003 and 2014 were selected, because heads larger than 28 mm were rarely used before 2003 in Scandinavia and no data on THAs performed after 2014 were available in the NARA dataset when the study was conducted. Only patients that had received a metal head of 28 mm, 32 mm or 36 mm on any type of polyethylene cup/insert were included. Dual-mobility cups were excluded. For patients operated on both hips, only the first operated hip was included. The application of the abovementioned selection and exclusion criteria resulted in 186,231 patients, grouped according to the head diameter used: 28 mm (101,094, 54%), 32 mm (57,853, 31%) and 36 mm (27,284, 15%) (Figure 14). The group with 32-mm heads was used as a reference. The mean age at primary THA was 70 (±10) years and 60%

(111,046 of 186,231) of the patients were women. There were differences between the groups in terms of the type of implant fixation, surgical approach and sex, as there was an accumulation of male patients with an uncemented THA performed through a posterior approach and shorter follow-up in the 36-mm group (Table 2).

Outcomes, follow-up and censoring

The outcomes of our study were revision for any reason and revision risk due to dislocation. Revision was defined as the exchange or removal of the entire implant or any of its parts. Patients were followed until their first THA revision and were censored at emigration, death, or December 31 2014, whichever came first.

Variables, survival analysis and truncation

The variable of primary interest was head size (28, 32 or 36 mm). Co-variables extracted from the NARA dataset included patient age, sex, date of primary THA, date of revision, cause of revision, type of prosthesis fixation, bearing material, type of surgical approach and type of polyethylene. (Table 3). Kaplan-Meier curves were drawn for each head size with the endpoints of revision for any reason and revision due to dislocation. The survival curves looked parallel up to 7 years and then crossed each other. At the same time point, the number of patients at risk dropped below 200 for the 36-mm group. The survival analysis was therefore truncated at 7 years in order to sustain the proportionality of revision risks across head sizes for a valid regression model (Figure 15). Cox multiple regression models were fitted to estimate the hazard ratio with 95% confidence intervals for all-cause revision and revision due to dislocation between the head sizes during the first 7 years of follow-up. 32-mm heads were used as the reference. Adjustments were made for patient age at index surgery, sex, year of surgery, type of cup and stem fixation, polyethylene type and surgical approach.

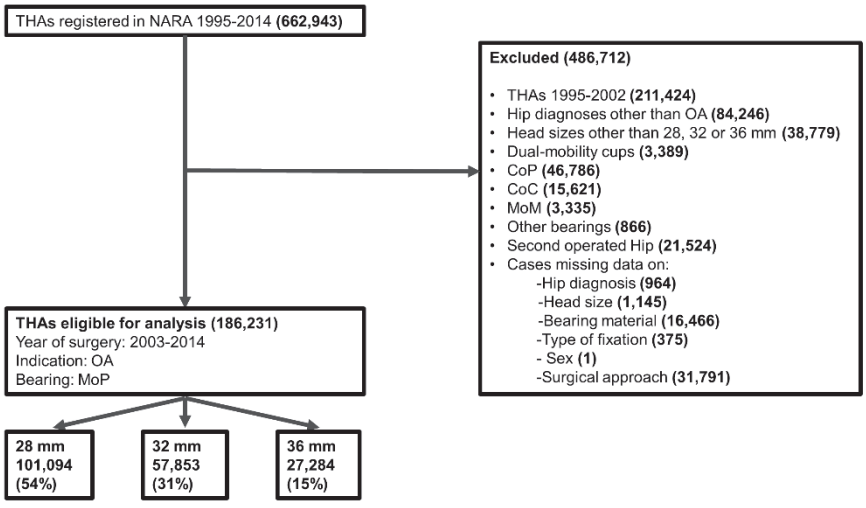


Figure 14. *Flowchart showing how the number of patients that were analyzed for the risk of revision due to dislocation and due to any reason was determined in Study I. NARA=Nordic Arthroplasty Register Association, OA=primary osteoarthritis, CoP=Ceramic on Polyethylene, CoC=Ceramic on Ceramic, MoM= Metal on Metal, MoP=Metal on Polyethylene*

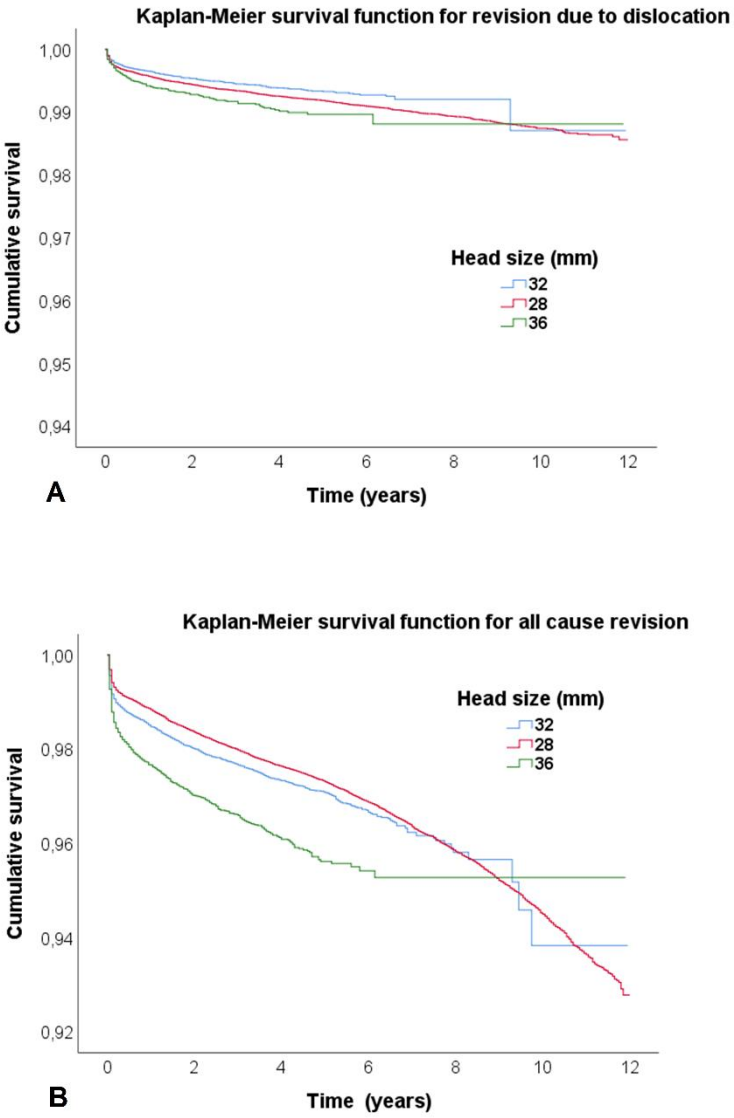


Figure 15. *Kaplan-Meier survival curves for revision due to dislocation (A) and for any reason (B). The curves were fairly parallel until the seventh year of follow-up and then crossed each other. The survival analysis was truncated at the seventh year.*

Table 2. Demographics and surgical details of patients analyzed in Study I

	Head size (mm)		
	28	**32**	**36**
Follow-up[a], years	7.0 (4.2-9.1)	2.8 (1.2-4.7)	2.1 (0.8-3.6)
Year of surgery[a]	2007 (2005-2009)	2012 (2010-2013)	2012 (2011-2014)
Age[b], years	70.8 (9)	70.1 (10)	68.9 (10)
Female (%)	62,644 (62)	35,325 (61)	13,077 (48)
Cemented cup (%)	86,617 (86)	39,672 (69)	3710 (14)
Cemented stem (%)	80,839 (80)	35,990 (62)	6695 (25)
Posterior approach (%)	52,325 (52)	35,785 (62)	25,379 (93)
MoUHMWPE[c] (%)	85,489 (85)	14,588 (25)	1409 (5)
MoXLPE[d] (%)	15,605 (15)	43,265 (75)	25,875 (95)

[a] median and interquartile range, [b] mean and standard deviation, [c] metal on non cross-linked polyethylene, [d] metal on cross-linked polyethylene.

Table 3. Variables in the NARA dataset used in Study I and Study II

Raw variables	**Levels of category**	**Additional proccessed variables**	**Levels of category**
Patient age at primary THA	continuous	Time to revision or censoring.	Continuous
Patient sex	Female/male	Cup fixation	Cemented/Uncemented
Date of primary THA	Date	Stem fixation	Cemented/Uncemented
Date of first revision	Date	Polyethylene type	Cross-linked Conventional
Cause of first revision	Aseptic loosening Deep infection Periprosthetic fracture Dislocation Pain only Other		
Fixation	Cemented Uncemented Hybrid Inverse hybrid Resurfacing		
Head material	Metal Ceramics Other		
Cup/Insert material	Metal Ceramics Cross-linked polyethylene Conventional polyethylene		
Surgical approach	Posterior Non-posterior		

3.2. STUDY II

Questions to be answered and hypothesis

A detailed description of the methodology is publicly available [138]. Study II sought to address the following question: Is the use of 36-mm heads in contemporary bearings associated with a reduced risk of revision and specifically revision due to dislocation compared with 32-mm heads, in patients who have undergone THA due to a femoral neck fracture? We hypothesized that the use of 36-mm heads would reduce the risk of revision due to dislocation.

Study design, patient selection and matching

Study II was designed as an observational, propensity-matched, register-based study. The methodology was fairly similar to that used in Study I regarding the variables extracted from the NARA database, but there were 5 main differences.

The study was conducted on patients that had undergone THA after a proximal femur fracture. (In the NARA database, patients with a femoral neck fracture cannot be distinguished from patients with any proximal femur fracture that has been treated with THA.)

28-mm heads were left out, as non-contemporary, and the study focused on the comparison between 32-mm and 36-mm heads.

The observation time was between 2006 and 2016 because 36-mm heads were hardly ever used before 2006 in Scandinavia.

Both metal and ceramic heads coupled with only XLPE were included, because the choice of head material was not expected to influence the risk of dislocation, at least in the short perspective. THA with conventional UHMWPE was left out, because it was rarely used after 2004.

Patients with 36-mm heads were matched with patients with 32-mm heads using a propensity score [78].

Starting with the 745,808 THAs registered in the NARA database between 1995 and 2016, patients that had undergone surgery due to a proximal femur fracture between 2006 and 2016 and had received either 32-mm or 36-mm heads in metal or ceramic on XLPE bearings were selected. As in Study I, DMCs were excluded and, in the event of bilateral THAs, only the hip operated on first was included. The selection process resulted in 12,476 patients. Looking at baseline characteristics (Table 4), it is obvious that patients with

36-mm heads were generally younger, included a higher proportion of males and underwent surgery using mainly a posterior approach with uncemented implant fixation. In order to reduce bias due to the confounding effects of the abovementioned factors, patients with 36-mm heads were matched with patients with 32-mm heads, based on their probability (propensity) of receiving a 36-mm head. Their propensity score was calculated based on their age, sex, type of approach and fixation, as well as bearing material. Patients were matched if their propensity score did not differ by more than 15% of the standard deviation in the mean propensity score, which is an acceptable calliper for reducing bias [7]. In the event of multiple matching, the patients with the closest propensity score were chosen (nearest neighbor method). Patients were matched at a 1:1 ratio and unmatched patients were discarded. 2,515 patients with 36-mm heads could be matched to 2,515 patients with 32-mm heads (Figure 16). The matching was evaluated by calculating the absolute standardized difference of the means or proportions of baseline demographics before and after matching (Table 5).

Outcomes, follow-up and censoring

The outcomes were revision for any reason and revision due to dislocation. Revisions were defined as in Study I. Patients were followed until their first THA revision and were censored at emigration, death, or December 31 2016, whichever came first.

Variables, survival analysis and truncation

The variable of primary interest was head size (32 or 36 mm). Co-variables included patient age, sex, date of primary THA, date of revision, cause of revision, type of prosthesis fixation, head material and type of surgical approach (Table 3). Kaplan-Meier survival curves were drawn for each outcome stratified by head size and were fairly parallel until 7 years (Figure 17). The number of patients at risk dropped under 100 for 36-mm heads at this time point and the survival analysis was therefore truncated at 7 years.
Univariable and multivariable Cox regression models were fitted to calculate the unadjusted and the adjusted hazard ratios, with 95% confidence intervals, for revision and revision due to dislocation, setting 32-mm heads as the reference. The choice of variables to adjust for was based on a directed acyclic diagram and its assumptions (Figure 18). According to this diagram, adjusting for age, sex, year of surgery and surgical approach would be enough to block

all measurable confounding pathways that could bias the effect of head size on the risk of revision.

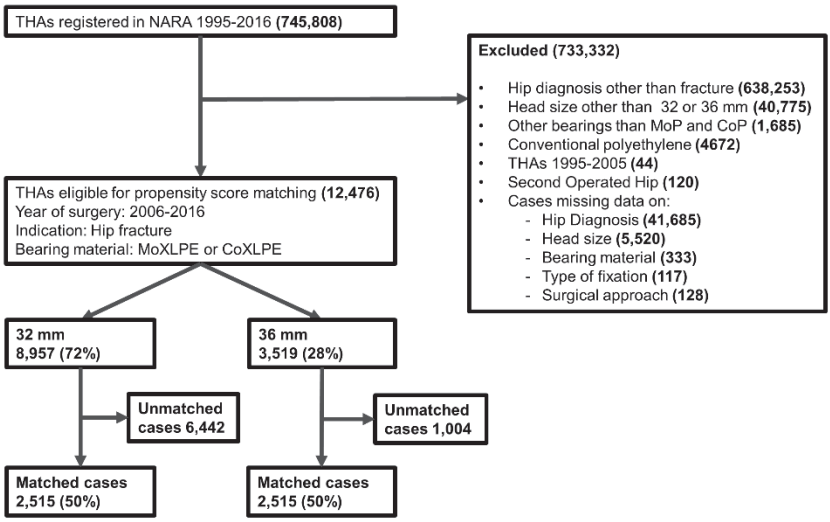


Figure 16. *Flowchart showing how the number of patients that were analyzed for risk of revision due to dislocation and due to any reason was determined in Study II. NARA=Nordic Arthroplasty Register Association, MoP=Metal on Polyethylene, CoP=Ceramic on Polyethylene, MoXLPE=Metal on highly cross-linked polyethylene, CoXLPE= Ceramic on highly cross-linked polyethylene*

Table 4. Demographics and surgical details of patient sample in Study II before propensity score matching (N=12,476)

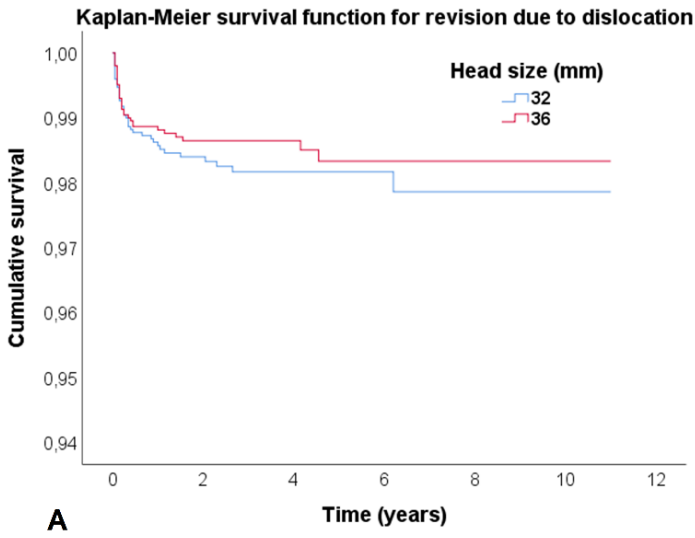
	Head size (mm)		
	32 (n=8,957)	**36 (n=3,519)**	**ASDM[a]**
Follow-up[b], *years*	2.4 *(1-4.4)*	2.3 *(1-4)*	0.1
Mortality *(%)*	1,702 *(19)*	621 *(18)*	0.04
Age[c], *years*	73 *(10)*	70 *(11)*	0.24
Year of surgery[b]	2013 (*2011-2015)*	2014 *(2012-2015)*	0.14
Female *(%)*	6,266 *(70)*	1,812 *(52)*	0.37
Cemented THA *(%)*	6,276 *(70)*	813 *(23)*	0.62
Cementless THA	1,219 *(14)*	1,729 *(50)*	0.71
Hybrid THA *(%)*	430 *(5)*	885 *(25)*	0.47
Reverse hybrid *(%)*	1,032 *(12)*	92 *(3)*	0.56
MoXLPE[d] *(%)*	7,954 *(89)*	3,083 *(88)*	0.04
CoXLPE[e] *(%)*	1,003 *(11)*	436 *(12)*	0.04
Post. Approach *(%)*	3,912 *(44)*	2,599 *(74)*	0.69

[a] absolut standarized difference in means, [b] median and interquartile range, [c] mean and standard deviation, [d] metal on cross-linked polyethylene, [e] ceramic on cross-linked polyethylene

Table 5. Demographics and surgical details of patient sample in Study II after propensity score matching (N=5030)

	Head size (mm)		
	32 (n=2,515)	**36 (n=2,515)**	**ASDM[a]**
Follow-up[b]*), years*	2.4 (*0.9-4.4)*	2.6 (*1.1-4.3)*	0.03
Mortality *(%)*	477 *(19)*	507 *(20)*	0.03
Age[c]*, years*	70 *(11)*	71 *(11)*	0.07
Year of surgery[b]	2013 *(2011-2015)*	2013 *(2011-2015)*	0.05
Female *(%)*	1,570 *(62)*	1,453 *(58)*	0.09
Cemented THA *(%)*	823 *(33)*	813 *(32)*	0.02
Cementless THA *(%)*	1,148 *(46)*	1,068 *(43)*	0.06
Hybrid THA *(%)*	428 *(17)*	542 *(22)*	0.11
Reverse hybrid *(%)*	116 *(5)*	92 *(4)*	0.06
MoXLPE[d] *(%)*	2,108 *(84)*	2,152 *(86)*	0.06
CoXLPE[e], *(%)*	407 *(16)*	363 *(14)*	0.05
Post. Approach *(%)*	1,724 *(69)*	1,705 *(68)*	0.02

[a] absolut standarized difference in means, [b] median and interquartile range, [c] mean and standard deviation, [d] metal on cross-linked polyethylene, [e] ceramic on cross-linked polyethylene



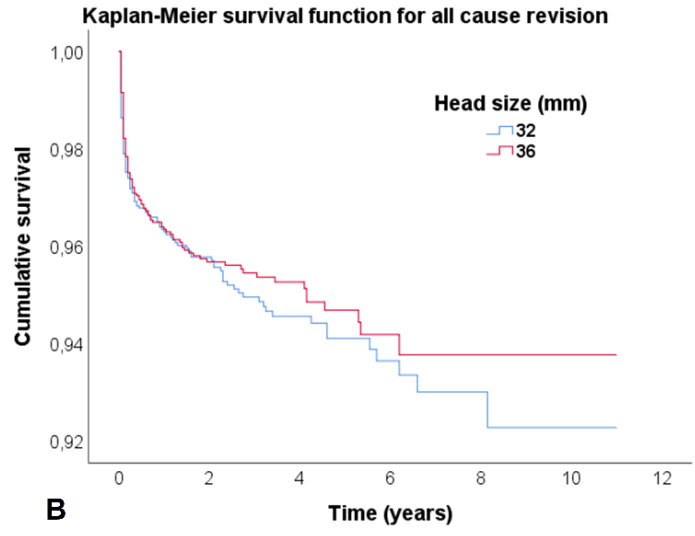


Figure 17. *Kaplan-Meier survival curves for revision due to dislocation (A) and for any reason (B). The curves were fairly parallel until the seventh year of follow-up. The number of patients at risk of revision dropped below 100 in the 36-mm group at 7 years and survival analysis was truncated at this time point.*

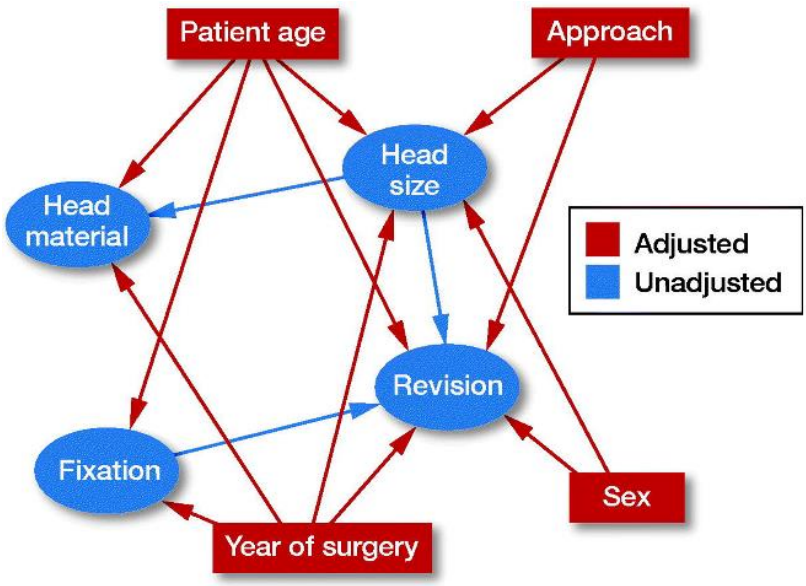


Figure 18. *Directed acyclic graph demonstrating why patient age, sex and year of surgery and surgical approach were selected as co-variables to adjust the Cox regression model. The graph is based on the following assumptions: 1) THA revision depends on head size, patient age, sex, year of surgery, surgical approach and type of fixation. The type of bearing does not affect the outcome, due to the short follow-up. 2) Surgeons operating on older patients, males, through a posterior approach and in more recently have probably chosen a 36-mm rather than a 32-mm head to reduce dislocation rates. 3) Younger patients, undergoing surgery more recently, have probably received an uncemented THA due to the popularization of this technique. 4) Surgeons have probably chosen a ceramic rather than a metal head when they use a 36-mm head in younger patients to prevent polyethylene wear and/or taper corrosion. Based on these assumptions, adjusting for patient age, sex, year of surgery and surgical approach is enough to block all recorded pathways that could confound the effect of head size on the risk of revision due to dislocation. Published in Acta Ortopedica 2020 [138].*

3.3. THE G7-RSA STUDY: GENERAL OVERVIEW

Studies III, IV and V are parts of the G7-RSA study, which is a randomized, controlled, single-blinded trial that had 2 aims. They were:

1) To evaluate the effect of the largest possible head size (36-44 mm) on polyethylene wear in MoVEPE bearings compared with 32-mm heads and
2) To evaluate cup fixation in terms of RSA cup migration when a novel cup surface is used compared with a well-established cup surface.

The study comprises 2 different interventions; one regarding the choice of head size and one regarding the choice of cup surface. To match the aims of this thesis, the intervention regarding the choice of head size was utilized. The presence of two different cup surfaces in the head size groups should theoretically not confound the effect of head size on the outcomes of the study since cup surface was randomly assigned. In this chapter, the part of the G7-RSA study which is common to Studies III-V is described, focusing on the intervention regarding head size.

Location, time settings and patient selection

The G-7 RSA has been conducted at two international centers; the Department of Orthopedic Surgery at Copenhagen University Hospital, Hvidovre, Denmark (CUH), and at the Department of Orthopedic Surgery at Sahlgrenska University Hospital, Mölndal, Sweden (SUH). Between December 2014 and February 2017, 722 patients were assessed for eligibility. The inclusion criteria can be summarized as follows.

- Patients with primary osteoarthritis that were scheduled to receive a unilateral cementless THA
- Age between 18 and 75 years with no severe comorbidities (ASA $\leq$ 3)
- Ability to speak and understand Danish or Swedish, depending on the center, as well as to give informed consent
- Ability to complete all postoperative controls up to 10 years

We excluded patients who had:

- Any hip pathology other than primary osteoarthritis, e.g. previous fracture or severe deformity
- Hip anatomy not suitable for standard implants
- Bone quality warranting cemented fixation

- Active medical treatment for osteoporosis
- Comorbidities that may alter pain perception (e.g. diabetes neuropathy)

- Acetabulum not a large enough to receive at least a 50-mm cup that can accommodate a 36-mm head
- Intraoperative need for screw fixation of the cup

Randomization

Ninety-six patients (48 at each center) were enrolled and randomized to receive either the largest possible (36-44 mm) head that could fit in the thinnest possible VEPE insert for the specific cup size or a standard 32-mm head (controls). They were also randomized to two different cup surfaces. In this way, half the patients in each head size group (largest possible or 32 mm) had one type of cup surface and half had the other. The allocation ratio was 1:1, resulting in 48 patients with the largest possible head (36-44 mm) and 48 patients with a 32-mm head (Figure 19).

Surgery and follow-up

Patients underwent surgery through either a posterior or a lateral approach, depending on the surgeon. The periacetabular bone and the proximal femur were marked with at least six 0.8-mm tantalum beads. The VEPE insert was marked with at least six 1.0-mm beads. All the implants came from the same manufacturer. All the patients received the same cementless femoral stem made of Ti-6Al-4V alloy and a modular cobalt-chromium head in sizes 32, 36, 40 and 44 mm. The cup was of the same design but with two different coatings; a porous titanium coating or a porous plasma spray. A range of cup sizes from 50-64 mm was available. All the patients received the same VEPE insert, which had an inner diameter from 32 up to 44 mm. The thinnest VEPE insert had an apical thickness of 4.7 mm and 4.3 mm at 45°. After surgery, the patients were followed up at three months and one and 2 years with RSA, a plain radiographic examination and patient reported-outcome measurements.

Radiologic assessment

RSA radiographs were acquired in a supine position with the hip unloaded, using 2 converging, ceiling-mounted roentgen tubes and a uniplanar calibra-

tion cage. The operated leg was placed parallel to the y-axis of the cage. All RSA radiographs were analyzed at CUH, using the model-based RSA software (version 4.2, RSAcore, Leiden, The Netherlands). Baseline RSA films were acquired within 24 hours after surgery and follow-up examinations were made at 3 months, one year and 2 years. The precision of RSA measurements was calculated as the 95% reference limit of the double examinations that were made at three months (the t critical value for the 5% level of statistical significance multiplied by the standard deviation of the difference in the double measurements from zero). Plain radiographs were acquired directly postoperatively and thereafter at one and 2 years. Plain radiographs were reviewed by two successive observers for signs of radiolucency around the cup. A radiolucency was present if the vertical distance between the cup surface and the acetabular bone was equal to or greater than 0.5 mm and extended to more than 50 % of a Charnley-DeLee zone (Figure 20). A radiolucency that was present in the directly postoperative radiograph was regarded as a gap. Gaps were regarded as being filled if they no longer fulfilled the radiolucency criteria in subsequent radiographs. A radiolucency that was not present in the directly postoperative radiograph but was present in subsequent examinations was regarded as an osteolysis. For the measurements of radiolucency, mDesk software (version 3.6.7.0, RSA Biomedical AB, Umeå, Sweden) was used.

Patient-reported outcomes

Patient-reported outcomes included hip function, health-related quality of life and activity level. Hip function was measured with the Harris Hip Score (HHS 0-100, with 100 showing best function) and the Oxford Hip Score (OHS 0-48, with 48 showing best function). Health-related quality of life was measured with the 3-level EQ-5D index (0-1, with 1 showing the best quality of life) and the visual analogue scale (EQ VAS) of the EQ-5D instrument (0-100, with 100 showing the best quality of life). The level of activity was measured with the University of California Level of Activity rank score (UCLA 1-10, with 10 showing the best activity level).

Sample size calculation

The study protocol included two sample size calculations, one for each aim. Regarding proximal head penetration, a difference of 0.07 mm between two groups was considered clinically relevant. Accounting for a standard deviation of 0.1 mm and a 5% level of statistical significance, at least 36 patients would

be required in each head size group in order to acquire 80% statistical power (two-sided, independent samples t-test). Regarding cup migration, a difference of 0.2 mm between two groups was considered clinically relevant. Accounting for a standard deviation of 0.3 mm and a 5% level of statistical significance, at least 33 patients in each group would be required to achieve 80% statistical power (two-sided, independent samples t-test). The enrollment of 48 patients in each head size group would allow for a 20% drop-out without losing statistical power.

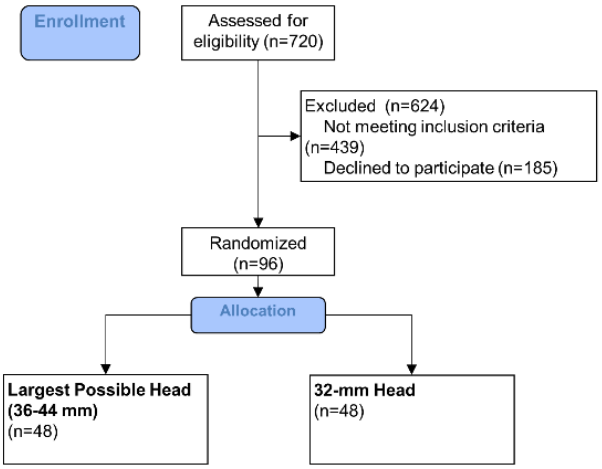


Figure 19. *Enrollment and randomization of patients in the G7-RSA study.*

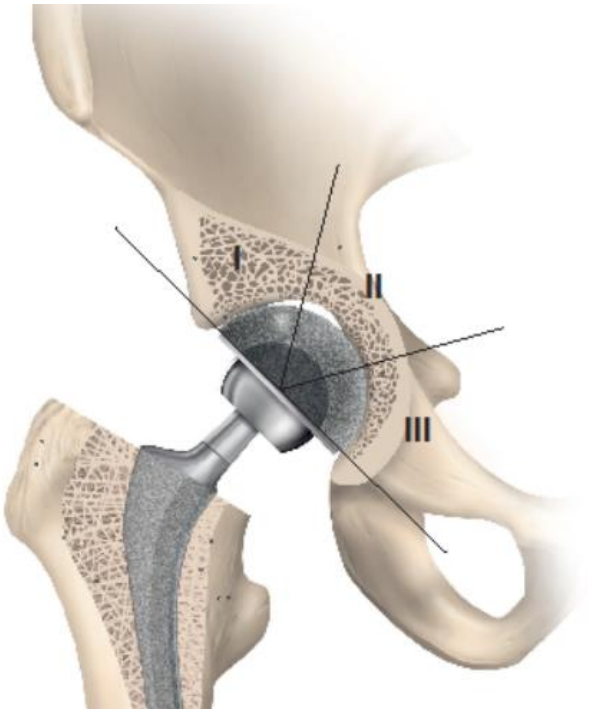


Figure 20. *The Charnley-DeLee zones around the cup.*

3.3.1. Study III. Head size and polyethylene wear

Study design, research question and hypothesis

Study III is a part of the G7-RSA study and is therefore a randomized, single-blinded, controlled trial. The question under investigation was whether the use of the largest possible metal head (36-44 mm) in the thinnest possible VEPE insert increases polyethylene wear compared with a standard 32-mm MoVEPE THA. We hypothesized that there is no difference in polyethylene wear between them.

Outcomes

The primary outcome was proximal head penetration along the Y-axis measured with RSA with an endpoint assessment at 2 years (Figure 21). Secondary outcomes were volumetric wear, the presence of periacetabular radiolucency in plain radiographs and patient-reported outcome.

Participant flow

Starting from 48 patients in each head size group, 44 of them were available for RSA assessment at 2 years (Figure 22). From the largest possible head group, 2 patients had been revised, one patient had withdrawn his/her consent and one did not come for the radiologic examination but sent in patient-reported outcome measurements. From the 32-mm group, 2 patients had been revised, one withdrew her/his consent and one had died for reasons unrelated to hip surgery.

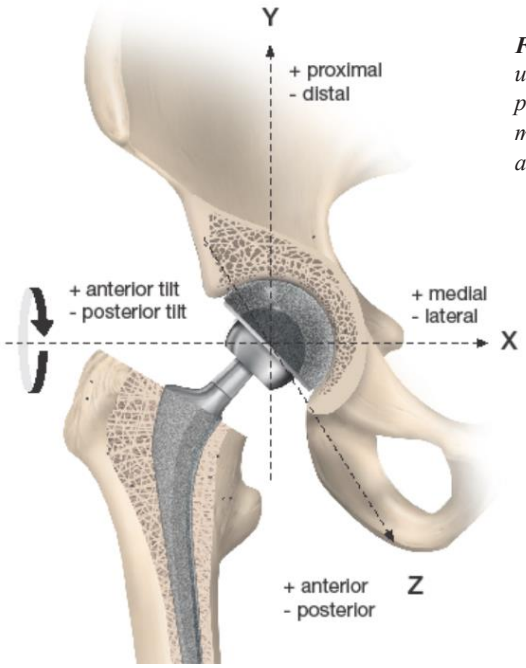


Figure 21. *The coordinate system used to measure proximal head penetration and proximal cup migration (along the Y-axis), as well as cup rotation around the X-axis.*

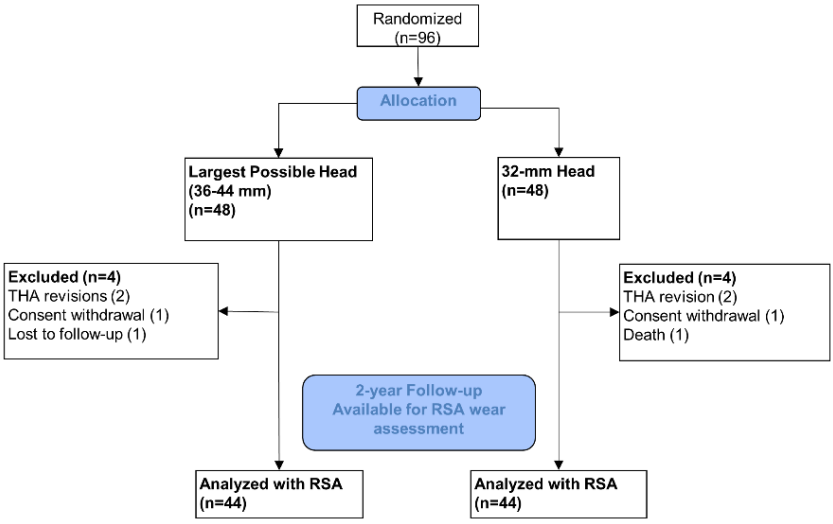


Figure 22. *Participant flow in Study III. The chart shows how the final number of patients that had their proximal head penetration measured with RSA at 2 years was determined.*

RSA measurement of polyethylene wear

For the measurement of proximal head penetration, a model-based method was used. A 3D cup model provided by the manufacturer was fitted in the RSA radiographs using edge detection algorithms. The modular head was also fitted using the same technique. Using baseline RSA radiographs as the reference, the translation of the center of mass of the head along the Y-axis of the cage relative to the center of mass of the cup was measured as proximal head penetration. Double measurements were available in all 86 patients. The RSA precision for proximal head penetration was 0.15 mm (0.13 mm at CUH and 0.18 mm at SUH). Volumetric wear was calculated as proximal head penetration times π times the square of head radius.

3.3.2. Study IV. Head size and blood metal-ion levels

Study design, research questions and hypothesis

Study IV is also a randomized, single-blinded, controlled trial that utilized the study participants in the G7-RSA study. The question addressed was whether patients with the largest possible metal head (36-44 mm) have higher blood levels of metal ions compared with patients with 32-mm metal heads. We hypothesized that they did.

Outcomes

The primary outcome of the study was whole-blood levels of cobalt, chromium and titanium measured at one and 2 years after THA. Should an elevated ion level be observed, the patient-reported outcome for patients with elevated ion levels would be compared that of patients with low ion levels using the OHS.

Participant flow

The outcomes in Study IV were not included in the G7-RSA trial protocol from the beginning but were added after the trial had begun. After additional ethical review board approval, whole-blood samples were collected at the one-and 2-year follow-ups. By the time additional ethical approval was granted, some patients had already reached their one-year follow-up and could therefore not leave blood samples until their second year of follow-up. Starting from 48

patients in each randomly allocated head size group at baseline, 34 patients with the largest possible head and 31 patients with the 32-mm head left blood samples at one year (Figure 23). At 2 years, the numbers were 41 and 37 patients respectively (Figure 24).

Blood ion level measurements

At CUH, 6 ml of whole blood were collected in ethylenediaminetetraacetic acid tubes, using the "Vacuette safety blood collection set and holder" (Greiner Bio-One GmbH, Austria). At SUH, 4 ml of whole blood were collected in sodium heparin tubes, using the "BD-Vacutainer system" (Becton, Dickinson and Company, UK). Both manufacturers assured that the needles used did not contain chrome, chromium or titanium. Blood samples were sent to an accredited laboratory in Sweden for analysis. Whole-blood ion levels were measured in µg/L. There was no lower detection limit for cobalt. For chromium, the lower detection limit was 0.5 µg/L, while it was 1 µg/L for titanium. We regarded metal-ion levels above 1 µg/L as elevated, based on the recommended threshholds for metal-on-polyethylene THA [49, 79].

Statistical sensitivity

The G7-RSA trial protocol did not include a sample size calculation based on metal-ion measurements, as they were not included in the initial outcomes of the trial. Nevertheless, the sample of 78 patients at the 2-year follow-up provides the study with enough statistical sensitivity to detect differences between groups of at least 0.30 µg/L for cobalt, 0.18 µg/L for chromium and 0.63 µg/L for titanium with 80% power and a 5% level of statistical significance (2-sided Mann Whitney test).

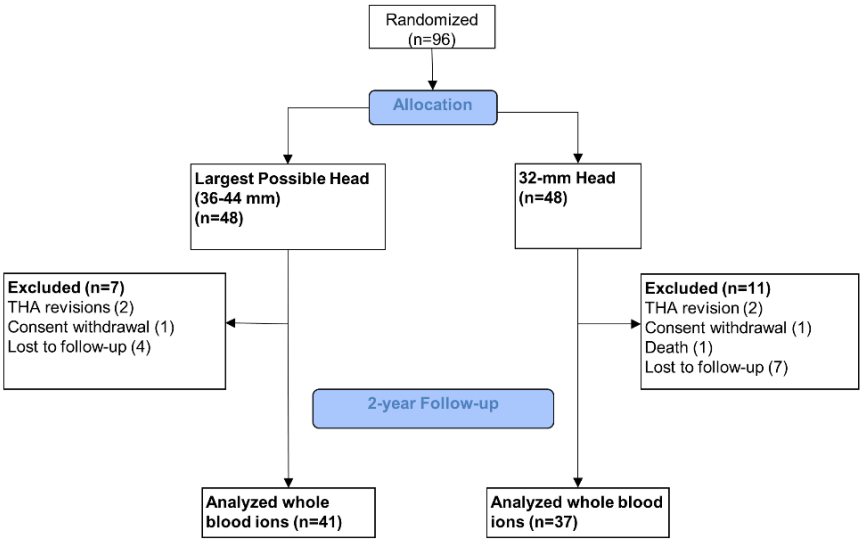


Figure 23. *Participant flow that shows how the final number of patients who had their blood-ion levels analyzed at the 1-year follow-up was determined.*

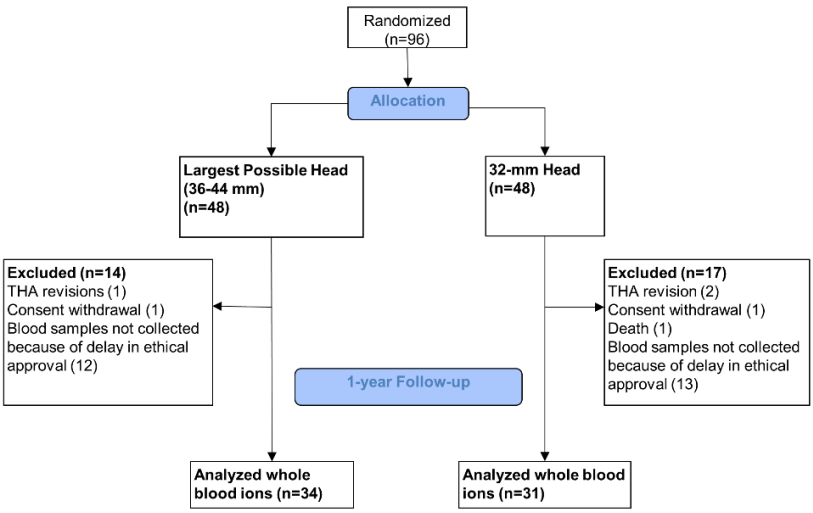


Figure 24. *Participant flow that shows how the final number of patients who had their blood ion levels analyzed at the 2-year follow-up was determined.*

3.3.3. Study V. Head size and cup fixation

Study design, research questions and hypothesis

Study V is a randomized, single-blinded, controlled trial as part of the G7-RSA study that focuses on early cup movement related to head size. The question that was addressed was whether the use of the largest possible head size (36-44 mm) in MoVEPE bearings could increase early cup movement and therefore jeopardize its fixation, due to the increased frictional torques observed in these bearings, compared with today's standard bearing size of 32 mm. We hypothesized that the use of the largest possible head increases early cup movement.

Outcomes

The outcome of the study was proximal cup migration along the Y-axis and cup rotation around the X-axis measured with RSA at 2 years.

Participant flow

At 2 years, apart from the 8 patients that had dropped out, as described in Study III, an additional 26 patients could not be assessed for RSA cup movement due to either too high CN or too few visible marker beads in the acetabular bone (Figure 25). Cup movement could therefore be compared between 30 patients with the largest possible head (36-44 mm) and 32 patients with a 32-mm head.

RSA measurement of cup movement

A model-based method was used to measure cup movement. At least three 0.8 mm beads, adequately scattered in the acetabular bone with a condition number (CN) ≤ 120 and with a mean error of rigid body fitting of ≤ 0.35, needed to be identified in the RSA radiographs in order to establish a valid reference bone model of the pelvis. A 3D cup model, derived from reverse engineering, was fitted using edge detection. Proximal cup migration was calculated as the translation of the center of mass of the cup model in relation to the reference bone model along the Y-axis of the cage (Figure 21). Cup rotation was calculated as the rotation of the center of the cup around the X-axis of the cage in relation to the reference bone model, as the latter was determined in the directly postoperative RSA radiographs. The precision of RSA measurements

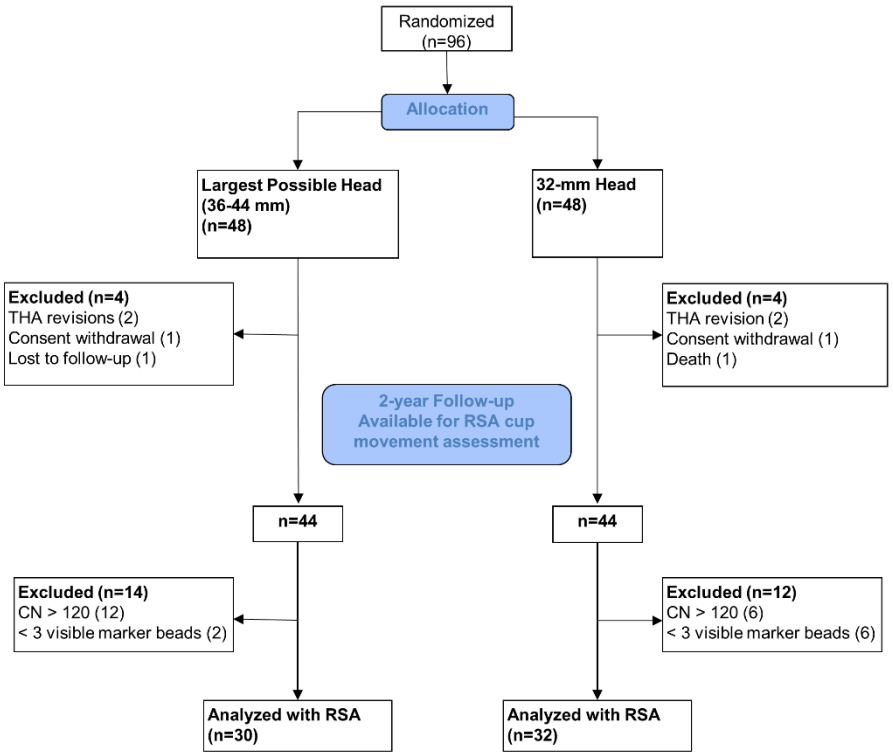


Figure 25. *Participant flow in Study V that shows how the final number of patients who had their cup movement analyzed with RSA at the 2-year follow-up was determined.*

was 0.2 mm (0.18 mm for CUH and 0.23 mm for SUH) for proximal cup migration and 1.1° (1.2° for CUH and 1.1° for SUH) for cup rotation.

3.4. STATISTICS

Nominal data were described with their frequency and percentage. Numerical data were described with their mean and standard deviation if normally distributed; otherwise, with their median and interquartile range. Statistical analyses were performed in SPSS, version 25 (IBM Corp, Armonk NY, USA)

and in R software, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). For all statistical inferences, the level of statistical significance was set at $\alpha = 0.05$. In Studies I and II, the Mantel-Cox log-rank test was used to compare the Kaplan-Meier survival curves. The validity of the Cox proportional hazards models was checked with Schoenfeld residuals. The propensity score in Study II was calculated using the "matchit" function in R software with a calliper set at 0.15. In Studies III-IV, numerical variables across the head size groups were compared using the Mann-Whitney test because they were not normally distributed. The statistical significance of prospective changes within each group was evaluated with the Wilcoxon signed-rank test. For comparisons of categorical data, the z-test or Fisher's exact test was used.

3.5. ETHICAL CONSIDERATIONS AND REGISTRATION

Studies I and II were approved by the regional ethical review board of Gothenburg (ID no: 858-16) in October 2016. The G7-RSA trial (Studies III-V) was prospectively registered at ClinicalTrials.gov (NCT02316704). Ethical approval was provided by the corresponding regional review boards in Denmark (ID no: H-4-2014-115) in November 2015 and Sweden (ID no: 972-14) in March 2015. Additional approval was granted regarding the collection of whole-blood samples for the measurement of metal-ion levels in September 2016.

In Studies I and II, written consent was not required from the study participants, as they were not exposed to any intervention. However, the study included the storage and processing of health data information. All patients undergoing THA had prospectively received written information regarding the storage of their operation data in the respective national arthroplasty register and they were informed that they could require the deletion of their health data at any time and without stating any reason. The administration of the registers contributing to the NARA is regulated by the local data protection authority in each Nordic country. Before merging the data from the 4 national joint registers, personal data were erased, making it impossible to connect them to individual patients.

In the G7-RSA study that comprised Studies III, IV and V, patients were exposed to a new intervention that included new implants and unusually large

head sizes that could potentially be associated with adverse events. Moreover, their marking with tantalum beads prolonged the surgical procedure and their follow-up exposed them to additional radiation and discomfort because of the RSA examinations and collection of blood samples. All the study participants received oral and written information about the risks of the study and gave their written consent prior to inclusion. Anonymity during data processing and exchange between the universities of Gothenburg and Copenhagen was guaranteed through de-identification and coding patient data that were only accessible to research administrators.

3.6. FUNDING

Studies I and II were partially funded by research grants from the Felix-Neubergh and the Hjalmar Svensson foundations. Institutional financial support has been received from Zimmer Biomet (Warsaw, IN, USA) for the recruitment of research participants in the G7-RSA study. Zimmer Biomet was not involved in the data process or preparation of the manuscripts that refer to the G7-RSA study.

4. RESULTS

4.1. HEAD SIZE AND RISK OF THA REVISION DUE TO DISLOCATION IN PATIENTS WITH PRIMARY HIP OSTEOARTHRITIS (STUDY I)

Between 2003 and 2014 and after censoring the survival analysis at 7 years, 1,324 (2.3%) patients with 32-mm heads had been revised for any reason, of which 295 (0.5%) were due to dislocation at a median follow-up of 2.8 years (iqr: 1.2-4.7). For patients with 28-mm heads, the numbers were 3,083 (3.0%) and 869 (0.9%) respectively at 7 years (iqr: 4.2-7.0). In patients with 36-mm heads, the median follow-up was 2.1 years (iqr: 0.8-3.6) and there were 819 (3.0%) revisions for any reason, of which 194 (0.7%) were due to dislocation. In all pairwise comparisons, the differences in revision rates due to dislocation reached statistical significance (Table 6). The 7-year Kaplan-Meier survival rates for revision due to dislocation exceeded 98% with small differences in favor of 32-mm heads (Table 6). In the multivariable Cox regression model, patients with 28-mm heads ran a 1.7 times (CI 1.4-2) higher risk of revision due to dislocation compared with 32-mm heads, while there was no statistically significant difference between 36- and 32-mm heads (HR: 0.9, CI 0.7–1), after adjusting for age, sex, year of surgery, surgical approach, implant fixation and type of polyethylene (Table 6). Interestingly, there was a higher risk of revision for any reason for 36-mm heads compared with 32-mm heads. Further analysis using the same multivariable Cox regression model but changing the outcome to revision due to aseptic loosening, prosthetic joint infection, periprosthetic fracture and pain revealed an increased risk of aseptic loosening with increasing head size from 28-mm (HR 0.8, CI 0.6-0.9) to 32-mm and then further to 36-mm heads (HR 2.3, CI 1.8–2.9).

Table 6. Summary of results of Study I.

		Head size in mm			P values		
Outcome		**28**	**32**	**36**	**28 vs 32**	**32 vs 36**	**28 vs 36**
Revision due to dislocation	Revisions (%)	869 (0.9)	296 (0.5)	194 (0.7)	<0.001	<0.001	0.02
	KM (CI)	99 (98.9-99.1)	99.2 (99.1-99.3)	98.8 (98.5-99.2)	<0.001	<0.001	
	HR (CI)	1.7 (1.4-2)	1	0.9 (0.7-1)	<0.001	0.09	
Revision for any reason	Revisions (%)	3083 (3)	1324 (2.3)	819 (3)	<0.001	<0.001	0.68
	KM (CI)	96.4 (96.2-96.5)	96.2 (96-96.5)	95.3 (94.8-95.8)	<0.001	<0.001	
	HR (CI)	1.1 (1-1.2)	1	1.14 (1.04-1.26)	0.2	0.01	

KM = Kaplan-Meier 7-year survival rate. HR = hazard ratio for the period 0-7 years, adjusted for age, sex, year of surgery, surgical approach, implant fixation and type of polyethylene. CI = 95% confidence intervals. P values refer to $\chi 2$ test for revision rates and Mantel-Cox log-rank test for KM survivals.

4.2. HEAD SIZE AND RISK OF THA REVISION DUE TO DISLOCATION IN PATIENTS WITH A FEMORAL NECK FRACTURE (STUDY II)

In the matched sample, between 2006 and 2016 and after censoring the survival analysis at 7 years, patients with 32-mm heads had a similar median follow-up time as patients with 36-mm heads, which was 2.5 years (1-4.4). In the group of 32-mm heads, there were 119 revisions (4.7%), of which 40 (1.6%) were due to dislocation. The corresponding numbers for 36-mm heads were 111 (4.4%) and 33 (1.3%) (Table 7). Kaplan-Meier survival did not differ statistically between the head size groups. The unadjusted and adjusted hazard ratios with their 95% confidence intervals were identical (Table 7). 36-mm heads demonstrated an HR of 0.8 (CI 0.5-1.3) for revision due to dislocation and 0.9 (0.7-1.2) for revision for all reasons.

Table 7. Summary of results of Study II.

		Head size in mm		
Outcome		**32**	**36**	**P value**
Revision due to dislocation	Revisions (%)	40 (1.6)	33 (1.3)	0.5
	KM (CI)	97.8 (97-98.7)	98.3 (97.6-99)	0.38
	HR (CI)	1	0.8 (0.5-1.3)	0.44
Revision for any reason	Revisions (%)	119 (4.7)	111 (4.4)	0.64
	KM (CI)	92.8 (91.2-94.4)	93.7 (92.2-95.2)	0.55
	HR (CI)	1	0.9 (0.7-1.2)	0.62

KM = Kaplan-Meier 7-year survival rate. HR = hazard ratio for the period 0-7 years, both unadjusted and adjusted for age, sex, year of surgery and surgical approach. CI = 95% confidence intervals. P values refer to χ^2 test for revision rates and Mantel-Cox log-rank test for KM survivals.

4.3. HEAD SIZE AND POLYETHYLENE WEAR (STUDY III)

Clinical outcome

Ninety-six patients with a median age of 63 years (56-69) were randomized to either head size group. Baseline demographics were balanced across the intervention and control group (Table 8). In the largest possible head group, 11 (23%) patients received a 36-mm head, 34 (71%) a 40-mm and 3 (6%) a 44-mm head. The median thickness of the VEPE insert was 4.7 mm (4.7-4.7) apically and 4.3 mm (4.3-4.3) at 45°. Two dislocations occurred in one patient and were treated with closed reduction. In three patients, stem subsidence was evident in the postoperative radiographs, but only one had clinical symptoms necessitating revision to a cemented stem. One patient had an early periprosthetic fracture and underwent stem revision. Finally, one patient complained of persisting groin/hip pain, which resolved after open exploration and excision of the trochanteric bursa.
In the 32-mm group, the median VEPE thickness was 8.7 mm (7.7-8.7) apically and 8.3 mm (7.3-8.3) at 45°. Dislocations occurred in three patients. One patient had 2 early postoperative dislocations, one patient had three and the third patient had one. The first two patients underwent THA revision, while the THA in the third patient remained stable after closed reduction. One patient had stem subsidence that stabilized and was treated conservatively (Table 9). Only patients that underwent revision of any implant part were excluded from the study.

RSA polyethylene wear

At 2 years, 44 patients with the largest possible head and 44 patients with a 32-mm head could be assessed with RSA for proximal head penetration (Figure 22). The total 2-year femoral head penetration (interquartile range) was -0.02 mm (-0.09 to 0.07) for the largest possible and -0.01 mm (-0.07 to 0.10) for the 32-mm group. Neither group had a proximal head penetration that differed statistically from 0 (p=0.55 and 0.53 respectively). The difference between the groups was not statistically significant either (p=0.32). There was no obvious bedding-in period in our sample for either group (Figure 26). In order for our results to be comparable with those of other studies, proximal head penetration was measured after excluding the initial 3-month period, resulting in 0.01 mm

for both groups that corresponds to a proximal head penetration rate of 0.006 mm/year. Accordingly, the volumetric VEPE wear rate was 6.1 mm3/year (-59 to 57) for the largest possible and 3.5 mm3/year (-21 to 34) for 32-mm heads, with no statistically significant difference between them (p=0.85).

Periacetabular radiolucencies and patient-reported outcomes

There were 12 patients with postoperative gaps between the cup and the acetabular bone. At 2 years, gaps were no longer visible in 11 patients, while they persisted in one patient (32-mm group) and were regarded as osteolysis by the independent evaluator. On the 2-year radiographs, 3 patients with the largest possible head and 7 patients with the 32-mm head had osteolyses (p= 0.31). The osteolyses did not have the classical appearance of scalloping like the ones typically observed years after the implantation of non-crosslinked polyethylene but appeared as a linear radiolucency that fulfilled the criteria of at least 0.5 mm width and extension to at least 50% of a Charnley-DeLee zone (Figure 27).
Patient-reported outcomes did not differ at baseline between the two head size groups. At 2 years, the response rates were 93% (41 of 44) for the largest possible head and 96% (42 of 44) for 32-mm heads. The patient-reported outcome increased postoperatively in both groups but did not differ between them at 2 years. The median Oxford Hip Score was 46 or higher, Harris Hip Score was 100 and the EQ-5D score was 0.97 in both groups, denoting excellent hip function and health-related quality of life. The median UCLA activity score was 7 in the largest possible head size group and 6 in the 32-mm group, but the difference was not statistically significant. When comparing patients with and without osteolyses at 2 years, no statistically significant differences were found in the Harris Hip Score, EQ-5D or EQ-VAS. There were statistically significant differences in the Oxford Hip Score and the UCLA activity score, but only the latter was clinically relevant, with a 2 ranks higher UCLA activity score in patients with osteolyses.

Table 8. Baseline demographics of patients in the G7-RSA study

	Largest possible head (n=48)	**32-mm head (n=48)**
Females	21 *(44)*	22 *(46)*
Median age in years *(IQR)*	62 *(55-67)*	65 *(59-71)*
Median BMI *(IQR)*	27 *(26-29)*	26 *(24-30)*
ASA group*		
1	23 *(50)*	19 *(40)*
2	21 *(44)*	26 *(54)*
3	3 *(6)*	3 *(6)*
Surgical approach		
Posterolateral	34 *(71)*	32 *(67)*
Lateral	14 *(29)*	16 *(33)*

Numbers are given as n (%) if not otherwise stated.
IQR=interquartile range, BMI=Body Mass Index, ASA=American Society of Anaesthesiologists.* Data about ASA were missing in one patient in the largest possible head group.

Table 9. Clinical outcome and adverse events related to the intervention

Adverse event (%)	**Largest possible head (n=48)**	**32 mm (n=48)**
1st time dislocation	1 (2.1)	3 (6.3)
Stem subsidence	3 (6.3)	1 (2.1)
Groin pain	1 (2.1)	0 (0)
Revisions		
Dislocation	0 (0)	2 (4.2)
Stem subsidence	1 (2.1)	0 (0)
Periprosthetic fracture	1 (2.1)	0 (0)
Total number of reoperations/revisions	**3 (6.3)**	**2 (4.2)**

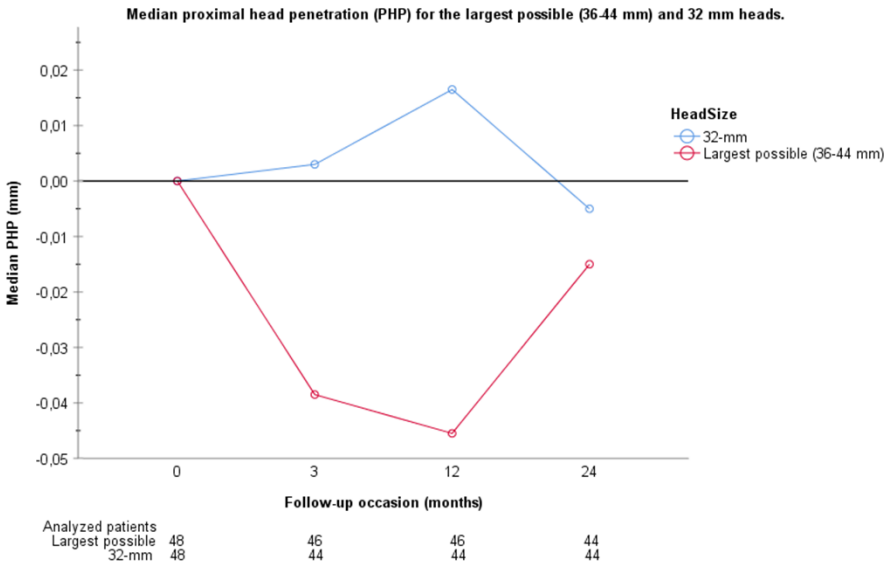


Figure 26. *Proximal head penetration at 3, 12 and 24 months. In contrast to most other studies assessing linear wear, no bedding-in period was observed for either head size group.*

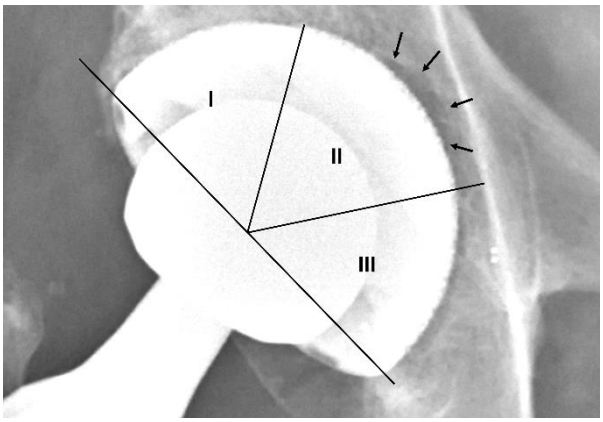


Figure 27. *A linear radiolucency in zone 2, observed on the 2-year radiograph, which was classified as osteolysis (arrows).*

4.4. HEAD SIZE AND BLOOD METAL-ION LEVELS (STUDY IV)

Results at 1-year follow-up

At one year, whole-blood ion level measurements were available in 34 patients with the largest possible head and 31 patients with 32-mm heads. The patients had similar demographics and implant characteristics (Table 10). In patients with the largest possible head, the median blood levels (interquartile range) were 0.12 µg/L (0.08-0.22) for cobalt, 0.50 µg/L (0.50-1.20) for chromium and 1.48 µg/L (1.14-1.87) for titanium. In patients with 32-mm heads, the values were 0.11 µg/L (0.08-0.15), 0.50 µg/L (0.50-0.59) and 1.58 µg/L (1.38-2.05) respectively (Figure 28).

Results at 2-year follow-up

At 2 years, blood-ion levels could be compared between 41 patients with the largest possible head and 37 patients with 32-mm heads. The patient demographics were still similar at 2 years, but there was some imbalance regarding the distribution of head length across the head size groups (Table 11). In the largest possible head group, cobalt levels were 0.18 µg/L (0.12-0.28), chromium 0.50 µg/L (0.50-0.57) and titanium 1.42 µg/L (1.01-1.72).

For the 32-mm group, the values were 0.15 µg/L (0.12-0.24), 0.50 µg/L (0.50-0.50) and 1.54 µg/L (1.16-1.87) respectively (Figure 29). Blood-ion levels did not differ statistically between the head size groups at either the one- or the 2-year follow-up (Table 12).

Results adjusting for head length

Increased head length has been associated with fretting, because it increases the stress at the taper-trunnion junction [46, 116]. The imbalance in head length shown in Tables 10 and 11 could possibly bias the results in favor of larger heads. To account for this, a multivariable linear regression adjusting for head length and stem offset (standard or lateralized) was performed, setting the whole-blood level for each ion as the outcome and the head size group as the variable of primary interest. The use of the largest possible head was still not

associated with increased metal-ion levels (Table 13). There was a statistically significant difference for chromium at one year that disappeared at 2 years.

Metal-ion levels and Oxford Hip Score

All whole-blood metal-ion values for cobalt and chrome were below 5 µg/L. At 2 years, one patient from the largest possible head group and two patients from the 32-mm head group had blood cobalt levels above 1 µg/L. The patient from the largest possible head group had cobalt levels of 1.69 µg/L, a cobalt/chromium ratio of 3.4, titanium levels of 1.66, an OHS of 48, and had received a 36-mm head on a standard offset stem with a head length of 0 mm. The first patient from the 32-mm group had cobalt levels of 3.38 µg/L, a cobalt/chromium ratio of 1.8, titanium levels of 1.52 µg/L, an OHS of 48 and had received a lateralized stem with a head length of +12 mm. The second patient had cobalt levels of 1.56 µg/L, a cobalt/chromium ratio of 3.1, titanium levels of 5.44 µg/L, an OHS of 46, and had received a stem with a head length of +6 mm. Additionally, a comparison of the Oxford Hip Score was made between patients with the 5 highest values and the remaining patients for each metal ion (Table 14). At the 1-year follow-up, patients with the 5 highest metal-ion values vs remaining patients had a median (min-max) cobalt level of 0.70 µg/L (0.52-1.3) vs 0.11 µg/L (0.05-0.50), chromium of 1.83 µg/L (1.50-2.08) vs 0.50 µg/L (0.50-1.38) and titanium of 3.36 µg/L (2.82-4.52) vs 1.50 µg/L (1-2.80). At the 2-year follow-up, patients with the 5 highest metal-ion values had cobalt levels of 1.56 µg/L (0.96-3.38) vs 0.16 µg/L (0.05-0.69), chromium of 1.49 µg/L(1.06-1.88) vs 0.50 µg/L (0.50-1.02) and titanium of 4.33 µg/L (3.06-6.74) vs 1.43 µg/L (1-2.79). The only clinically relevant difference was found at 2 years in patients with the 5 highest titanium levels, who had an 8 points lower Oxford Hip Score compared with the remaining patients.

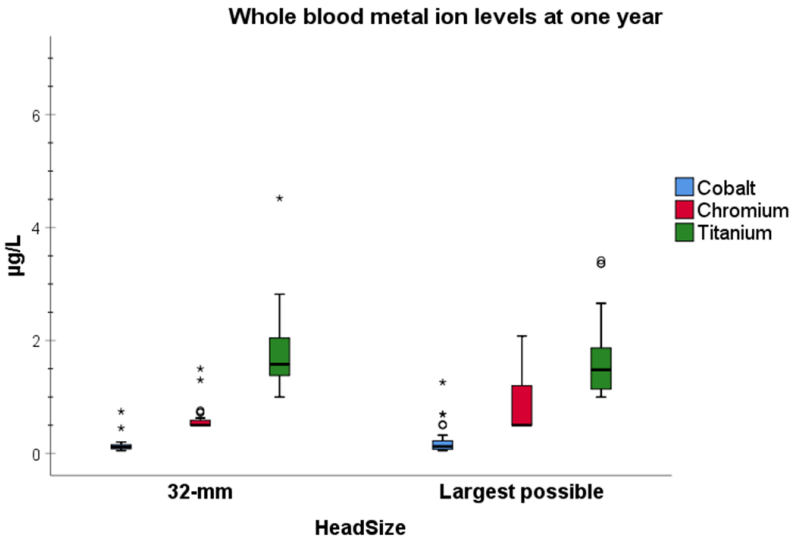


Figure 28. *Box plot of metal-ion levels at the 1-year*

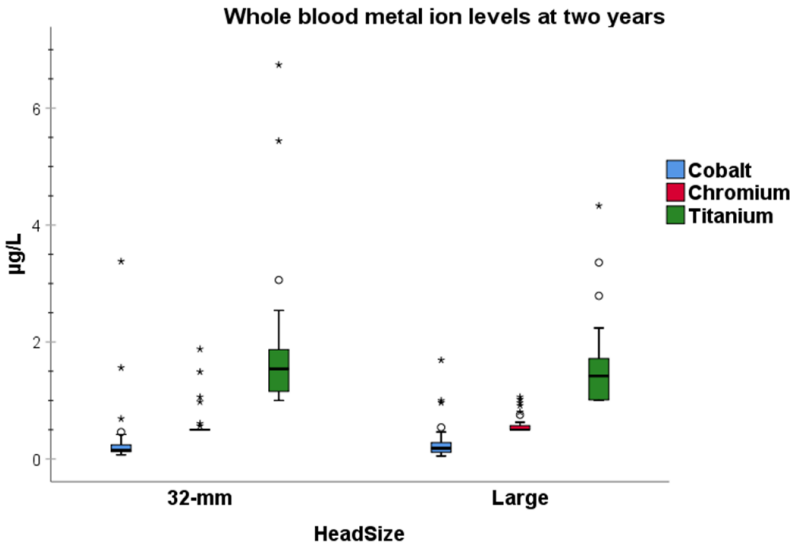


Figure 29. *Box plot of metal-ion levels at the 2-year follow-up.*

Table 10. Demographics of patients with metal ion measurements at the 1-year follow-up

	Largest possible head (n=34)	**32-mm head (n=31)**
Females	15 (44)	14 (45)
Median age in years (IQR)	62 (53-65)	65 (61-70)
Median BMI (IQR)	28 (26-29)	27 (25-31)
ASA group*		
1	17 (52)	10 (32)
2	15 (45)	18 (58)
3	1 (3)	3 (10)
Surgical approach		
Posterolateral	20 (60)	16 (52)
Lateral	14 (41)	15 (48)
Cup Surface		
Type I	17 (50)	16 (52)
Type II	17 (50)	15 (48)
Head length		
-6 mm	3 (9)	4 (13)
-3 mm	6 (18)	6 (19)
0 mm	17 (50)	10 (32)
+3 mm	7 (20)	3 (10)
+6 mm	0 (0)	7 (22)
+9 mm	1 (3)	0 (0)
+12 mm	0 (0)	1 (4)
Stem offset		
Standard	18 (53)	19 (61)
Lateralized	16 (47)	12 (39)

Numbers are given as n (%) if not otherwise stated.
IQR=interquartile range, BMI=Body Mass Index, ASA=American Society of Anaesthesiologists. * Data about ASA were missing in one patient in the largest possible head group.

Table 11. Demographics of patients with metal ion measurements at the 2-year follow-up

	Largest possible head (n=41)	**32-mm head (n=37)**
Females	18 (44)	17 (46)
Median age in years (IQR)	61 (55-66)	66 (59-69)
Median BMI (IQR)	28 (26-29)	26 (24-30)
ASA group*		
1	20 (50)	12 (32)
2	17 (43)	22 (60)
3	3 (7)	3 (8)
Surgical approach		
Posterolateral	27 (66)	22 (60)
Lateral	14 (34)	15 (40)
Cup Surface		
Type I	21 (51)	19 (51)
Type II	20 (49)	18 (49)
Head length		
-6 mm	3 (7)	4 (10)
-3 mm	8 (19)	5 (14)
0 mm	21 (51)	11 (30)
+3 mm	6 (16)	4 (10)
+6 mm	2 (5)	12 (33)
+9 mm	1 (2)	0 (0)
+12 mm	0 (0)	1 (3)
Stem offset**		
Standard	25 (61)	20 (55)
Lateralized	16 (39)	16 (45)

Numbers are given as n (%) if not otherwise stated
IQR=interquartile range, BMI=Body Mass Index, ASA=American Society of Anaesthesiologists. * Data about ASA were missing in one patient in the largest possible head group. ** Data about stem offset were missing in one patient in the 32-mm group.

Table 12. Comparison of whole blood ion levels at the 1- and the 2-year follow-ups

	Largest possible head (36-44 mm)	**32 mm head**	**Difference**	**p***	**Follow-up**
Cobalt	0.12 (0.08-0.22)	0.11 (0.08-0.15)	0.01	0.54	
Chromium	0.50 (0.50-1.20)	0.50 (0.50-0.59)	0	0.06	1 year (n=65)
Titanium	1.48 (1.14-1.87)	1.58 (1.38-2.05)	-0.10	0.38	
Cobalt	0.18 (0.12-0.28)	0.15 (0.12-0.24)	0.03	0.67	
Chromium	0.50 (0.50-0.57)	0.50 (0.50-0.50)	0	0.55	2 years (n=78)
Titanium	1.42 (1.01-1.72)	1.54 (1.16-1.87)	-0.12	0.21	

Values are given in µg/L. Medians (interquartile range). * Mann Whitney U-test

Table 13. The results of the multivariable linear regression after adjustment for head length and type of stem at the 1- and the 2-year follow-ups.

	Coefficient*	CI	p	Follow-up
Cobalt	0.08	-0.03 to 0.18	0.16	1 year (n=65)
Chromium	0.27	0.08 to 0.47	0.01	
Titanium	-0.02	-0.34 to 0.29	0.88	
Cobalt	0.05	-0.15 to 0.25	0.61	2 years (n=78)
Chromium	-0.03	-0.16 to 0.09	0.58	
Titanium	-0.19	-0.59 to 0.21	0.34	

* Difference in whole blood ion levels (µg / L) when the largest possible head is used instead of 32 mm adjusting for head length (-6, -3, 0, +3, +6, +9, +12 mm) and stem type (standard or lateralized). CI= 95% confidence intervals of the coefficient.

Table 14. Comparison of the Oxford Hip Score between patients with the 5 highest whole blood ion levels for each ion and the remaining patients at the 1- and the 2-year follow-ups.

Metal ion	OHS of the 5 highest values	OHS of remaining patients	Difference	Follow-up
Cobalt	44 (34-47)	46 (23-48)	-2	
Chromium	47 (27-48)	46 (23-48)	1	1 year (n=65)
Titanium	45 (32-48)	46 (23-48)	-1	
Cobalt	46 (42-48)	46 (20-48)	0	
Chromium	47 (37-48)	46 (20-48)	1	2 years (n=78)
Titanium	39 (37-46)	47 (20-48)	-8	

OHS=Oxford Hip Score. Values for OHS are given in medians (min-max).

* Mann Whitney U-test

4.5. HEAD SIZE AND CUP FIXATION (STUDY V)

2-year RSA cup migration

At the 2-year follow-up, 30 patients with the largest possible head could be compared with 32 patients with 32-mm heads, assessing RSA cup migration (Figure 25). Both groups demonstrated a statistically significant proximal cup migration ($p<0.001$), (Figure 30). For the largest possible head group, the median proximal cup migration was 0.15 mm (0.09–0.31), with 43% of them exceeding 0.2 mm. For 32-mm heads, the proximal cup migration was 0.20 mm (0.04-0.35), with 53% of them exceeding 0.2 mm ($p=0.44$). The difference in proximal cup migration between the groups was not statistically significant ($p=0.69$). In terms of cup rotation around the X-axis, both groups demonstrated a statistically significant posterior tilt of 0.44° (-0.20° to 0.84°), $p=0.02$, for he largest possible head group, and 0.23° (-0.02° to 0.77°), $p=0.03$, for the 32-mm group (Figure 31). The difference between them was not statistically significant either ($p=0.62$).

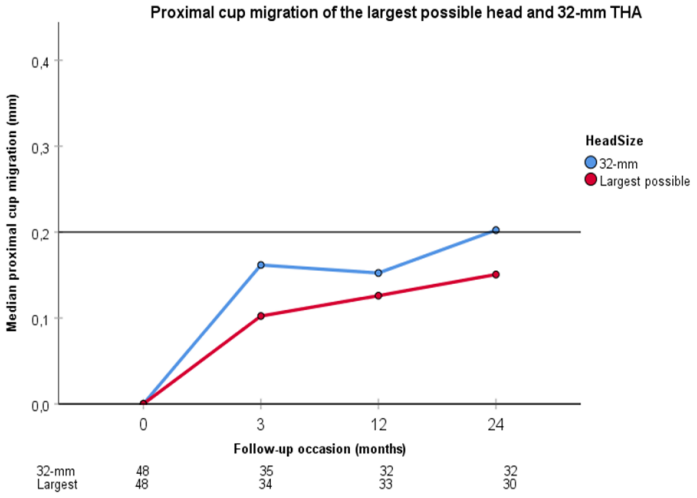


Figure 30. *Proximal cup migration along the Y-axis for patients with the largest possible head size and patients with a 32-mm head. In patients with 32-mm heads, proximal cup migration reached the threshold of 0.2 mm at 2 years. For patients with the largest possible head, proximal cup migration was smaller, but it did not differ statistically from patients with 32-mm heads.*

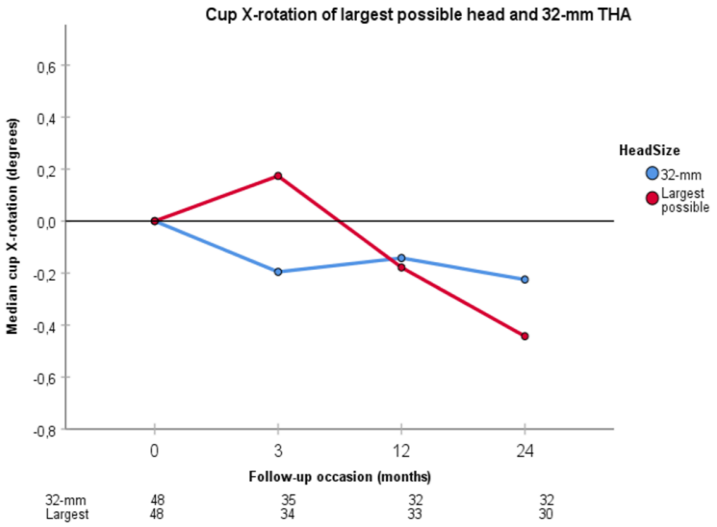


Figure 31. *Cup rotation around the X-axis for patients with the largest possible head size and patients with 32-mm heads. Both groups demonstrated a posterior cup tilt (negative cup rotation) at 2 years, but it did not differ to a statistically significant level.*

5. DISCUSSION

Head size in THA is a current topic of discussion at every orthopedic meeting. In the age of conventional UHMWPE, head size was limited by the adverse events of polyethylene wear. After the introduction of XLPE, wear became less troublesome and head sizes of 32 mm or even larger emerged and have been introduced in routine clinical care, reflected in recent national register reports [139]. The gradual increase in head size over the past few decades has coincided with a decrease in dislocation rates [56, 68] and there is good preclinical evidence in terms of increased impingement-free range of motion [27] and jumping distance [123] that advocates the use of larger heads as an effective way of increasing THA stability. In clinical settings, the effect of larger heads on dislocation rates has been confirmed for head sizes up to 32 mm, but it has been difficult to show a further decrease in dislocation rates for even larger heads. This is probably because the gain in impingement-free hip range of motion reaches its maximum with head sizes approximating 38 mm [15], and there is a lack of studies comparing specifically 32-mm heads with larger ones. On the other hand, long-term register reports indicate that metal heads larger than 36 mm coupled with XLPE are inferior compared with smaller or ceramic heads [6, 110]. It remains unclear whether the problem is related to XLPE wear or taper corrosion [126]. Higher frictional torque has been reported in larger metal-on-XLPE bearings [125], which could provide a third mechanism of THA failure through torque transmission to the cup/bone interface and subsequent cup migration. As a result, dislocation, polyethylene wear, taper corrosion and cup migration are important aspects for the longevity of THA, related to head size.

5.1. HEAD SIZE AND DISLOCATION IN PATIENTS WITH OSTEOARTHRITIS (STUDY I)

Interpretation of own results

In patients undergoing THA for the indication of primary osteoarthritis, we found a 1.7 times higher risk of revision due to dislocation when 28-mm heads were used instead of 32-mm heads. A further increase to 36 mm was associated with a marginally decreased hazard ratio (0.9) that did not reach statistical significance and could therefore not be generalized at population level. On the other hand, 36-mm heads were associated with a 2.3 times higher risk of revision due to aseptic loosening. This association was also noticed in the transition from 28 mm to 32 mm, but at a considerably lower magnitude (HR 1.25).

Limitations and methodological considerations

The results of Study I should be examined in the light of its inherent limitations due to lack of randomization. There were imbalances in the patient- and surgery-related risk factors that may have confounded the effect of head size on the risk of dislocation. For example, patients with 36-mm heads comprised a lower proportion of females, mainly underwent surgery using a posterior approach, with the uncemented technique and highly cross-linked polyethylene. In contrast, patients with 28-mm heads were mainly females, undergoing surgery using the cemented technique, conventional UHMWPE and with a lower proportion using the posterior approach. The accumulation of the abovementioned risk factors in the 36-mm group may have had a negative effect on its unadjusted estimates of revision risk due to dislocation (Table 2). These imbalances were taken into account in the multivariable Cox regression model, which altered the revision risk due to dislocation in favor of 36-mm heads, although the difference was minimal and did not reach statistical significance. The median follow-up also differed among the head size groups. 28-mm heads had a considerably longer follow-up, which, combined with the use of conventional UHMWPE, could allow for complications such as aseptic loosening and late dislocations to become evident. However, these complications were not expected in patients with 32-mm heads and especially 36-mm heads who had a median follow-up below 3 years and an overrepresentation of highly cross-linked UHMWPE. This makes it more difficult to explain the increased revision risk due to aseptic loosening found

in patients with 36-mm heads as the effect of head size alone. There may be other, unrecorded risk factors accumulated in this group that bias the results for 36-mm heads, such as the lack of information about patient comorbidities, implant position and the surgeon's preoperative assessment of dislocation risk that may also have affected the choice of head size. If surgeons chose the largest possible head size for patients they had assessed as running a higher risk of dislocation or other causes of THA failure in order at least to reduce the risk of dislocation, the results for 36-mm heads could be negatively skewed due to selection bias. Another limitation is that the NARA database does not register non-operated dislocations and the true dislocation rates therefore remain unknown. Revisions due to dislocation are instead used as a proxy to estimate dislocation rates. However, not all dislocations lead to revisions, as approximately as many as half of them can be permanently treated with closed reduction [48, 111]. Finally, the NARA database is unable to distinguish non-posterior approaches, such as direct anterior, lateral and anterolateral, because one of the four national registers contributing to the NARA reports the surgical approach as posterior or non-posterior. The posterior approach has been identified in most studies as an independent risk factor for dislocation, but as yet any differences between non-posterior approaches have not been reported [100, 153].

Synthesis of own results with literature

Our results in patients with osteoarthritis confirm that the transition from 28 mm to 32 mm has been followed by a decrease in revisions due to dislocation. Similar results have previously been reported from the national registers contributing to the NARA, with a 1.25 to 4 times higher risk of revision due to dislocation in THAs with heads smaller than 32 mm [17, 59, 75]. These studies have included a case mix of hip diagnoses and have an observation period from 1987, the earliest [17], to 2010, the latest [75]. Their results could therefore be difficult to apply specifically to osteoarthritis patients undergoing surgery in modern times. Study I gives the results from a more recent period (2003-2014) that can be generalized to patients with hip osteoarthritis. There is one study from the Dutch Register with settings comparable to those in Study I. Zijlstra et al. [153] reported a 1.6 times higher risk of revision due to dislocation when 28-mm heads were used instead of 32 mm. For this reason, our results, as well as the results of other register-based observational studies, have shown a fairly clear benefit for 32-mm heads over 28 mm in terms of increased THA stability. It would be logical to assume that using 36-mm heads rather than 32 mm would benefit the THA stability even more. However, this assumption has been only

sparsely investigated. Apart from Study I and the study from the Dutch Register, there are no other register-based studies comparing 32-mm heads with 36-mm ones. We found no difference between them, while Zijlstra et al. found a 0.6 times lower risk of revision due to dislocation in 36-mm heads but only when the posterior approach was used. Interestingly, both studies reported a higher risk of revision for reasons other than dislocation in 36-mm heads. Acknowledging that both studies suffer from the inherent limitations of observational studies in terms of bias due to unmeasured confounding, as well as a short follow-up, a cause-effect relationship between the use of 36-mm heads and inferior THA survival is difficult to assume. The current evidence is therefore insufficient to either support or discourage the use of 36-mm heads over 32 mm in routine primary THA. There is evidence supporting the use of 36- to 40-mm heads in revision THA [53], as well as the use of anatomic head sizes, like those found in hip resurfacing, large MoM THA and DMC THA [61, 77, 99]. These bearing combinations, especially large MoM and hip resurfacings, suffer from other complications, such as loosening, periprosthetic fractures and pseudotumors, and their use has declined and they are hardly ever used in routine hip replacement. To date, DMC THA with cross-linked polyethylene has not demonstrated any severe complications, but it lacks long-term follow-up and RCTs comparing it with contemporary 32- or 36-mm THA.

Clinical implications

The use of 32-mm heads over 28-mm heads has increased THA stability in patients undergoing surgery for the indication of osteoarthritis. The use of 36-mm heads over 32 mm does not appear to be equally beneficial and it remains uncertain whether their use provides a dislocation-preventing effect size that overcomes their potential long-term inferiority in MoXLPE bearings.

5.2. HEAD SIZE AND DISLOCATION IN PATIENTS WITH FEMORAL NECK FRACTURE (STUDY II)

Interpretation of own results

In patients with a femoral neck fracture that underwent THA, the difference in revision rates between 32-mm and 36-mm heads was only 0.3% for both revision due to dislocation and revision for any reason. Both the unadjusted and the adjusted survival analysis was in favor of 36-mm heads, with a hazard ration of 0.8 that did not reach statistical significance and corresponded to such a low absolute risk difference that, in addition to generalizability, probably also lacks clinical relevance.

Limitations and methodological considerations

Study II has limitations similar to those in Study I. It is also an observational study, in which the potential accumulation of unrecorded risk factors, such as comorbidities, implant position and the surgeon's preoperative assessment of dislocation risk in the 36-mm group, could negatively confound a potential dislocation-preventing effect by this head size. Moreover, all proximal femoral fractures that have been treated with THA are registered in the NARA database as fractures. The majority of them should be displaced femoral neck fractures, as it is the only fracture type routinely treated with THA. Some cases of intertrochanteric or pathologic fractures may also have been treated with THA. These rare cases may have run a higher risk of dislocation. The NARA database is unable to distinguish between different types of proximal femoral fractures. It is unlikely that these fractures are overrepresented in either head group. There were also imbalances in the known confounders across head sizes, but this limitation was addressed by matching 32-mm and 36-mm patients according to their propensity for receiving a 36-mm head, based on sex, age, year of surgery, method of fixation and type of head material. The result was a good match with the highest absolute standardized difference of means at 0.11 (Table 5), which is below the 0.15 threshold for significant heterogeneity [7]. Propensity score matching increased the internal validity of the study, as it made the groups more comparable, but at the expense of external validity. The sample size dropped from 12,476 patients before matching to 5,030 patients, which had a considerable impact on the statistical

sensitivity of the study. With the numbers given, Study II had the statistical sensitivity to detect differences in revision rates of a minimum of 1%. Nevertheless, the observed differences of 0.3% were too small to be considered clinically relevant. A median follow-up time of 2.5 years is short, but it is long enough to capture revisions due to dislocation. Sixty-nine of the 73 observed revisions due to dislocation had occurred by the median follow-up.

Synthesis of own results with literature

Our results for patients with a THA after a femoral neck fracture point in the same direction as other reports regarding the role of head size. Very few studies have been performed solely on patients with femoral neck fractures. Jameson et al. [67] compared overall revision risks in 4,323 patients with a femoral neck fracture, undergoing surgery between 2003 and 2010, with different head sizes divided into four groups; < 28 mm, 28 mm, 30 or 32 mm and ≥ 36 mm. There was no significant difference (HR 0.79, p=0.5) when 28-mm heads were used compared with other groups. The outcome of the study was overall revision, but 37.5% of the revisions were due to dislocation and head size was not found to be a predictor. Instead, cementless fixation was a predictor of revision (HR 1.3, p=0.02). Cebatorius et al. [22] studied 1,512 THAs after a femoral neck fracture undergoing surgery between 2011 and 2013 and compared 28-mm heads with 32 mm. They reported that the posterior approach was a predictor of revision due to dislocation (HR 2.3, p=0.04) but not head size (p=0.4). The abovementioned studies do not make comparisons between contemporary head sizes and may, especially the latter, be underpowered. Hoskins et al. [63] compared the risk of revision due to dislocation among 8,582 patients with 32-mm or smaller heads, 5,820 patients with 36-mm or larger heads and 1,778 patients with bipolar heads in DMCs. All patients had been operated due to a femoral neck fracture. The risk was lower for 36-mm or larger heads compared with 32-mm or smaller heads (HR=0.6, CI 0.4-0.8). The risk was also lower for bipolar heads but only during the first 3 months of observation (HR=0.3, CI 0.1-0.7). The study did not report the distribution of smaller than 32-mm and larger than 36-mm heads and included all bearing combinations. The NARA has recently reported a lower risk of revision due to dislocation (HR 0.4, CI 0.3-0.6) when anatomic heads in DMCs were used compared with 32- or 36-mm heads as one group in a propensity score-matched analysis of 9,040 patients with a femoral neck fracture [70]. Patients with DMCs had higher mortality rates, denoting the possible selection of patients with higher morbidity running a higher risk of dislocation in this group. So, based on observational studies, including Study II, it is difficult to demonstrate an

association between head size and reduced risk of revision due to dislocation when 32-mm femoral heads are compared with 28-mm or 36-mm femoral heads. In patients with a femoral neck fracture, as in patients with osteoarthritis [77], a reduction in dislocation rates only became evident when larger heads were group together or when head size approached anatomical values, as in DMCs. One possible explanation could be that large heads in DMCs could provide a greater dislocation-preventing effect size (than adjacent larger heads) that overcomes the negative confounding effect of comorbidities and other risk factors that usually accumulate in larger heads in observational studies. For this reason, when a higher risk of dislocation is anticipated, the choice of a 36-mm head over a 32 mm is not expected to address instability issues as adequately as an anatomic head size in a DMC. It could also be argued that the lack of long-term results in contemporary DMCs is probably of less importance considering the shorter life expectancy of patients with femoral neck fractures. However, the lack of long-term follow-up, as well as the slightly higher price of DMCs, should be taken into account when considering them for patients with primary osteoarthritis.

Clinical implications

In patients at high risk of THA dislocation, such as patients undergoing surgery due to a femoral neck fracture, the choice of a 36-mm head over a 32-mm head is probably unable to address instability. In such cases, when a high risk of dislocation is anticipated, other options, like the use of bipolar heads in DMCs, are probably a better option than 36-mm heads.

5.3. HEAD SIZE AND POLYETHYLENE WEAR (STUDY III)

Interpretation of own results

Linear wear rates, measured with RSA proximal head penetration, were very close to zero for both the largest possible and 32-mm heads. Most measurements were below the upper detection limit (0.13-0.18 mm) of the RSA examination, which is the most probable explanation of the small negative and positive values that clustered around zero (Figure 26). Volumetric wear rates were also very small and did not differ between the head size groups. For this reason, the results of Study III did not demonstrate any impact of head size on VEPE wear in this short-term report. The study also investigated the presence of periacetabular radiolucencies, as well as patient-reported outcomes between the head size groups, and found no differences. Interestingly, there was a slightly higher Oxford Hip Score by 2 points in patients with osteolysis at two years, but the difference cannot be considered clinically relevant, as it was below the minimally important difference of 5 points of this score [9]. There was also a 2 ranks higher UCLA activity level in patients with radiolucencies. Given the short follow-up, the presence of radiolucencies could hardly be explained as the effect of polyethylene wear. It could be speculated that more active patients put a greater load on their cups and increase the mechanical stress at the cup-bone interface that, along with increased joint fluid spikes, could increase periacetabular bone turnover and result in radiolucencies [101].

Limitations and methodological considerations

The interpretation of the study's results should be viewed under the lens of its limitations. RSA measurements were unable to distinguish between proximal head penetrations below 0.13 mm at CUH and 0.18 mm at SUH. The use of a model-based approach was the only way to perform measurements. A marker-based approach could have increased the precision of the measurements [109], but this was not possible, because the markers implanted in the thin polyethylene were not visible in the vast majority of cases, as they were covered by the radiopaque shadows of the cementless cups and large heads. Previous studies assessing head penetration using RSA have reported similar precisions ranging from 0.13 mm [128] to 0.17 mm [89]. The follow-up in the current study is short. Modern polyethylene inserts have reduced linear wear

rates to 0.02 mm/year [51], making the detection of differences in linear wear within such a short time improbable, unless the intervention group has a clear inferiority. However, the in-vivo impact of large metal heads on VEPE wear has not previously been investigated. This makes the 2-year follow-up a reasonable endpoint, in order to detect any potential short-term inferiority of large metal heads in terms of VEPE wear. The study also reports on the clinical outcome in terms of adverse events, such as dislocations and reoperations. The report of adverse events is only descriptive and cannot be generalized, as the study is not sufficiently powered for this purpose. Plain radiographs were reviewed by two successive observers, without the opportunity for both of them to review all radiographs. It was therefore not possible to estimate the inter-observer error. The presence of osteolysis in 10 of 88 patients at only 2 years may be overestimated, considering that all patients have received a modern VEPE, but the potential overestimation of osteolysis would not be expected to affect the comparative groups in an unbalanced way.

Synthesis of own results with literature

The in-vivo effect of larger heads in polyethylene wear has been investigated in non-vitamin E XLPE using different methods, as previously described in the introduction to this thesis. Most studies report on head penetration or linear wear rates and only a few report on volumetric wear, which is probably a better estimate of polyethylene wear, since a constant head penetration corresponds to a larger volume and thereby the mass of polyethylene debris in larger heads [16]. Our results relating to head penetration rates in MoVEPE bearings appear to agree with those in other in-vivo studies, which have investigated head penetration rates of different sizes of metal or ceramic heads on non-vitamin E XLPE inserts. They have also reported values very close to zero (< 0.02 mm/year) and no differences between head sizes up to 40 mm [20, 64, 83]. One study has compared VEPE wear caused by 32-mm or 36-mm ceramic heads and reported linear wear rates below 0.02 mm/year as well [90]. One interesting difference in Study III, compared with the abovementioned, is the absence of a "bedding-in" period. One possible explanation could be a more stable locking mechanism between the cup and the insert or possibly different plastic properties in the thin VEPE insert, suggesting a smaller creep margin. This specific cup and locking mechanism has not been used in RSA studies before and it would be interesting to see if its unique "bedding-in behavior" can be reproduced in other RSA studies or if it is the result of "noise" created by the low RSA precision relative to the small head penetration measurements. Volumetric wear rates have been reported to be almost double for larger heads,

regardless of the type of head material. Lachiewicz et al. [83] have reported 26 mm3/year for 36- to 40-mm MoXLPE bearings versus 13 mm3/year for 32 mm. Howie et al. [64] have reported 14 mm3/year for 36-mm ceramic heads on XLPE versus 7 mm3/year for 32 mm. Study III is the first to investigate in-vivo polyethylene wear between the largest possible (36-44 mm) and the contemporary 32-mm head in MoVEPE bearings and it reports even lower volumetric wear rates of 6.1 mm3/year vs 3.5 mm3/year respectively. The trend towards almost double values of volumetric wear for larger heads is consistent with the abovementioned literature. However, the difference found in Study III was not statistically significant and the reported volumetric wear rates of XLPE are clearly below the previously suggested threshold of 80 mm3/year. This threshold is probably an extrapolation of the 0.1 mm /year threshold for conventional UHMWPE [23] to 32-mm heads. However, to date, there are no known thresholds for wear rates that can be applied for XLPE, as no complications related to XLPE wear have as yet been reported. Radiologic studies of XLPE and VEPE THA have reported none, up to 6 years' follow-up [90, 108], or very small osteolytic lesions, up to 14 years' follow-up, with no association between head size and osteolysis [83]. Study III is in line with the absence of the latter association but has a much shorter follow-up. For this reason, the small differences in volumetric wear rates related to head size appear to lack clinical relevance in contemporary THA comprising metal or ceramic heads on XLPE or VEPE inserts.

Clinical implications

The use of heads larger than contemporary metal heads coupled with VEPE inserts as thin as 4.3 mm, has not increased polyethylene wear, but the follow-up is too short to allow for any definite conclusions about the safety of their use.

5.4. HEAD SIZE AND WHOLE-BLOOD METAL IONS (STUDY IV)

Interpretation of own results

In Study IV, all the measured metal-ion values were very low and did not differ between the head size groups. The use of the largest possible metal head size up to 44 mm in MoVEPE bearings did not generate a higher dissemination of cobalt, chromium and titanium ions in blood. Hip function, measured with the Oxford Hip Score, in patients with higher measurements of cobalt and chromium levels, did not differ from those with lower levels. Patients with higher titanium levels reported a lower median Oxford Hip Score. It is uncertain whether this is an early sign of future corrosion-related complications, and it needs to be investigated when longer-term results of the study become available.

Limitations and methodological considerations

Several limitations should be mentioned. A considerable number of patients (25) were not able to leave blood samples at the 1-year follow-up because ethical approval was delayed. At 2 years, 11 patients did not leave blood samples for unknown reasons. The abovementioned patients could be a source of bias if their blood-ion levels differed across the head size groups. At 1 year, an equal number of patients from each head size group did not leave blood samples, but their reported hip function was comparable to that of those who gave blood samples (Table 15). At 2 years, the 4 missing patients from the largest possible head group had a lower hip function than the missing patients with 32-mm heads. Whether this difference reflects a difference in metal-ion levels or other reasons for inferior hip function remains unknown. As a result, the number of patients with missing metal-ion values are probably not a major source of bias. The study did not measure preoperative metal-ion levels. Patients may have had different baseline values for metal ions, depending, for example, on the presence of other metal ion-generating implants. As a result, a prospective analysis of metal-ion changes could not be made but only a cross-sectional analysis between the head size groups. Since the study is randomized, any potential difference in preoperative metal-ion values would only be by chance. The study used metal-ion levels as an estimate of corrosion, but it is not possible to verify corrosion because no patients were revised due to complications related to corrosion. MRI scans that could help diagnose

complications related to corrosion, such as pseudotumors, are not available. The study can therefore make associations between head size and whole-blood metal ions but not between head size and corrosion. Finally, the follow-up is too short for the study of corrosion. Symptoms of taper corrosion, such as pain, swelling and loss of hip function, usually appear later than 2 years [25, 120]. However, the timespan to clinical metal-ion elevation as a manifestation of corrosion is unknown. Finally, the study measured whole-blood ion levels but not serum levels. The measurement of serum-ion levels is more common and is probably a safer way of measuring ion levels, because of the lower risk of contamination, but it provides a less complete estimate of the actual blood metal ion-levels because metals concentrate in erythrocytes [94].

Table 15. Comparison of patients with missing blood-test in Study IV at 1 and 2 years.

	Largest possible head (36-44 mm)	**32 mm head**	**Follow-up**
No blood-test (%)	12 (26)	13 (30)	1 year
OHS	46 (45-48)	45 (38-47)	
No blood-test (%)	4 (9)	7 (16)	2 years
OHS	35 (22-47)	48 (46-48)	

OHS = Oxford Hip Score given in median (min-max).

Synthesis of own results with literature

Head size, metal ions and corrosion

The role of large metal heads in the pathogenesis of fretting wear and corrosion in the taper-trunnion interface in MoP THA remains controversial. In a retrieval analysis of 59 prostheses with 28-mm and 13 prostheses with 36-mm metal heads, Dyrkacz et al. reported equal ratios of fretting and corrosion between them, but corrosion was more severe in 36-mm heads [40]. In another retrieval study, Del Balso et al. matched 23 32-mm metal heads with 23 28-mm heads with the same taper design, head length and stem offset, and reported greater fretting but the same corrosion scores for 32-mm heads [33]. In a recent systematic review of 46 cases of gross trunnion corrosion, the head size was 28 mm in one case (2%), 32 mm in three (8%) and 36 or 40 mm in 42 cases (90%) [8]. Finally, a study from the Australian registry reported a 3.2 times higher risk of revision due to adverse reactions to metal debris in patients with 36-mm or larger metal heads compared with 32-mm or smaller in metal-on-cross-linked polyethylene THA [31]. The positive association between head size and fretting and corrosion has been questioned by several other studies. Plummer et al. reported on 27 MoP THAs that had been revised because of adverse local tissue reactions secondary to taper-trunnion corrosion. In 20 (74%) of them, the head size was 28 or 32 mm, while, in 7 (26%) cases, the head size was 36 or 40 mm [120]. Triantafyllopoulos et al. retrieved 154 MoP THAs including head sizes from 22 to 44 mm and found that head size was not associated with fretting and corrosion [136]. Instead, shorter taper designs, mixing different alloys and longer time of implantation were risk factors. Siljander et al. retrieved 92 MoP THAs with a head diameter of 28, 32 and 36 mm. Head size had a weak negative association with fretting and corrosion. On the other hand, BMI, male sex, varus malalignment of the stem and length of implantation were positively correlated to fretting or corrosion [129]. The abovementioned retrieval studies have utilized a visual system for the identification and classification of the severity of fretting and corrosion, such as the Goldberg system [57]. Another retrieval study used a quantitative method to estimate material loss from the taper, expressed as maximum linear corrosion depth, and reported no differences between matched measurements in 28- and 32-mm metal heads with the same taper design and similar head length and length of implantation [142]. Using a similar methodology, no difference in material loss from the taper was found between retrieved 36-mm and > 40-mm metal-on-metal THA [84]. The abovementioned studies are observational and all but three [33, 142] have not controlled for other factors that may confound any potential effect of head size on fretting and corrosion,

such as stem offset, head length, taper design or length of implantation. In Study IV, metal-ion levels were compared between two randomly assigned head size groups with the same taper design, same length of implantation and comparable patient characteristics in terms of BMI and sex distribution. Increased head length and increased stem offset have been identified as risk factors for corrosion in a study with quantitative assessment of corrosion [34] but not in a study with qualitative assessment of corrosion [85]. Study IV controlled for imbalances in head length and stem offset and still found no differences in metal-ion levels at the 2-year follow-up. Very few studies have compared metal-ion levels between different head sizes and, specifically in metal-on-polyethylene THA, only 2 studies could be identified. In a randomized, controlled trial, cobalt, chromium and titanium levels did not differ between 28- and 36-mm heads in metal-on-metal THA at the 2-year follow-up [44]. The same study reported 2-year serum cobalt levels (0.14 µg/L) for 28-mm metal on polyethylene bearings similar to those found in Study IV for both head size groups. White et al. reported on 12 patients with 32-mm MoP and 18 patients with 36-mm MoP THA at a mean follow-up of 5 years [146]. Detectable cobalt-ion levels were found in 3 (25%) patients with 32-mm heads averaging 0.7 µg/L, compared with 14 (78%) patients with 36-mm heads averaging 2.9 µg/L. The same study was unable to detect cobalt levels in patients with ceramic heads regardless of their size. Craig et al. reported higher blood cobalt levels at 5 years for 36- and 40-mm heads compared with 28-mm heads in a cohort of 43 patients with the same uncemented hip implant. In all groups, cobalt levels were below 1 µg/L [26]. Dover et al. repeated the measurements in 33 patients at 10 years and reported increased cobalt levels for all head sizes over time, but no statistically significant differences between them (0.64, 1.4 and 1.1 µg/L for 28-, 36- and 40-mm heads respectively) [39]. Study IV included a much larger sample and compared 32-mm heads with even larger sizes but did not find any difference. Should metal-ion levels be a reliable indicator of corrosion, the results of Study IV support the studies that have not found an association between head size and corrosion.

Patients with metal ions above reported thresholds

The values of cobalt and chromium levels in Study IV were far below the previous suggested thresholds of 7 or 5 µg/L [1, 2]. At 2 years, 75 of the 78 patients had values below the even more stringent threshold of 1 µg/L for metal-on-polyethylene bearings [49, 79]. The three patients that exceeded this threshold had excellent hip function (OHS ≥46), despite a reported positive predictive value of 96% for the threshold of 1 µg/L regarding the risk of

corrosion [49]. Moreover, selecting the patients with the 5 highest metal-ion values still did not demonstrate any decrease in OHS at 2 years. Interestingly, the median cobalt levels found in Study IV (0.15-0.18 µg/L) were lower than or similar to the levels reported in healthy individuals without hip implants. The serum cobalt concentration in non-THA patients has been reported at 0.24 µg/L [124] or 0.14-0.16 µg/L [44], depending on the study. The absence of a correlation between increased metal-ion levels and patient-reported hip function in Study IV has also been reported by White et al. [146]. This highlights the importance of a clinical evaluation of patients with elevated metal-ion levels. Their measurement could be a useful tool in the differential diagnosis of an underperforming MoP THA, but increased metal-ion levels without any loss of hip function could be difficult to interpret.

Clinical implications

Despite the increased frictional torques and bending moments, generated by the large metal heads, the use of the largest possible metal heads in MoVEPE bearings does not cause any elevation of blood metal-ion levels compared with 32-mm heads. Until 2 years postoperatively, blood metal ions remain at low levels, comparable to those of patients without hip implants. The use of large metal heads does not appear to predispose patients to trunnion-taper corrosion, but a longer follow-up is required, because corrosion is a time-dependent adverse event.

5.5. HEAD SIZE AND CUP FIXATION (STUDY V)

Interpretation of own results

In Study V, patients with the largest possible head had 0.05 mm less proximal cup migration and 0.21° more rotation along the X-axis (posterior tilt) than 32-mm heads, but the differences were very small and lacked statistical significance. There are no known thresholds for cup rotation, but a difference of only 0.21° could hardly be considered clinically relevant. The small difference in proximal cup migration was in favor of the largest possible heads. Their 2-year proximal cup migration did not exceed the threshold of 0.2 mm suggested by Pijls et al- [119]. It should, however, be remembered that the suggested thresholds for implant migration are derived from meta-analyses after comparing the 2-year migration data from RSA studies with the 10-year survival data in long-term survival reports [119, 144]. The suggested threshold for cups may be specific to the specific cup designs included in the meta-analysis and it is a question of whether it can be generalized for any cup design. This has been demonstrated for some stem designs that failed the suggested 2-year subsidence threshold but still exhibited excellent 10-year survival [133]. The difference in cup migration between the head size groups, rather than separately comparing the cup migration within each group with a questionable threshold, is probably a better method for studying the effect of head size on cup fixation. However, it remains unclear which difference in cup migration has a predictive value for future cup loosening. Considering that every increase of 1 mm in 2-year cup migration is associated with a 10 % increase in the 10-year revision risk, the difference of only 0.05 mm found in Study V probably lacks clinical relevance. So, using the largest possible head was not associated with early cup fixation.

Limitations and methodological considerations

The limitations in Study V include the increased number of dropouts from the 2-year RSA assessment, the precision of RSA measurements and the use of only 2 cup designs. The sample size calculation accounted for 20% dropouts, but due to difficulty acquiring valid RSA measurements of cup migration in a considerable number of patients, the dropouts increased to 35%. This reduced the statistical sensitivity of the study and 0.22 mm became the lower limit for statistically significant cup migration between the head size groups.

Nevertheless, it maintained sufficient statistical power to detect a proximal cup migration of at least 0.05 mm within a head size group, which is below the suggested 0.2 mm threshold [119] that predicts a future increased risk of revision due to loosening. The reason the study maintained sufficient statistical power, despite many dropouts, was that the standard deviation in the 2-year RSA measurements for proximal cup migration was three times lower (0.1 mm) than the one used in sample size calculation (0.3 mm). The reason for the invalid RSA measurements was inadequate scattering of the RSA marker beads in the acetabular bone, along with an inability to visualize at least 3 markers because of the cup-head shadow. Moreover, the precision of the RSA proximal migration was 0.2 mm (0.18 mm and 0.23 mm for CUH and SUH respectively), which means that Study V was unable to distinguish between values lower than these limits. The RSA precision was still comparable with that in other studies that have applied a markerless protocol for the measurement of proximal cup migration and has been reported as being between 0.16 mm [122] and 0.3 mm [130], for example. A marker-based approach would probably have increased the precision [152], but it was not possible to apply this kind of protocol because of difficulty identifying the markers implanted in the insert, as they were hidden by the large metal heads and the cementless cups. Finally, the study was performed on 2 different cup designs which limits the generalizability of the results to these specific cups. On the other hand, limiting the study to only two cup designs that were randomly assigned between the head size groups increased the internal validity of the results, as it is highly improbable that cup design would be able to confound the effect of head size on cup migration.

Synthesis of own results with literature

The results of Study V cannot be compared with those of other clinical trials because there are no other studies that have investigated the in-vivo effect of head size on cup migration. In preclinical trials, Scholl et al. [125] reported increased frictional torques with increasing head sizes (22, 26, 28, 32, 36, 40 and 44 mm) for MoUHMWPE, MoXLPE and CoXLPE but not for CoC bearings. Menengini et al. [98] found increased frictional torques when heads larger than 32 mm were used in MoXLPE but not in CoXLPE bearings. They also reported higher frictional torques when VEPE instead of XLPE inserts were coupled with 32-mm metal or ceramic heads. Jahnke et al. [66] reported larger micromotions in the interface of cementless cups and foam bone when higher frictional torques were applied. Alonso et al. [5] reported higher stress in the cortical bone-cement interface when head size increased from 28 mm to

32 mm and then 36 mm, in a finite element model using cemented cups. The abovementioned in-vitro studies suggest a positive association between head size and frictional torque that may possibly become even greater when metal heads are coupled with VEPE inserts and could jeopardize cup fixation. Study V is the first to test this hypothesis in a clinical setting and it was unable to confirm it, as it found no association between early cup fixation up to 2 years and head size.

Clinical implications

Large metal heads up to 44 mm could be used in MoVEPE THA without compromising early cup fixation.

6. CONCLUSIONS

- **Paper I** The transition from 28-mm to 32-mm heads in routine MoP THA in patients with primary osteoarthritis in the Nordic countries has been associated with a decrease in the risk of revision due to dislocation. The risk of revision for all reasons has remained unchanged. A further increase in head size from 32 mm to 36 mm has not been accompanied by a further decrease in the risk of revision due to dislocation. The use of a 32-mm head should be regarded as standard in routine MoP THA.
- **Paper II** The use of 36-mm heads rather than 32-mm heads in patients with a femoral neck fracture has not been associated with a decrease in the risk of revision due to dislocation in the Nordic countries. In order to further reduce the risk of dislocation in fracture patients, other surgical technique or implants choice options should be considered rather than increasing head size to 36 mm.
- **Paper III** The use of the largest possible cobalt-chromium head (36-44 mm) in the thinnest possible vitamin E highly cross-linked polyethylene (down to 4.3 mm) does not increase polyethylene wear rates during the first 2 years compared with 32-mm heads. Moreover, the presence of radiolucencies and patient-reported outcomes are equal between the abovementioned patient groups. Short-term polyethylene wear is therefore not a concern when 36-mm or larger heads are indicated.
- **Paper IV** Up to two years postoperatively, the use of the largest possible cobalt-chromium head (36-44 mm) on a titanium alloy trunnion does not increase the whole-blood ion levels of cobalt, chromium and titanium compared with 32-mm heads. Neither metal-ion levels nor patient reported-outcomes indicate any THA malfunction due to corrosion when the largest possible metal head is used. The safety of large heads needs to be reevaluated when longer-term results are available.
- **Paper V** The presumed increase in frictional torque generated by the largest possible heads (36-44 mm) in cementless metal-on-vitamin-E highly cross-linked polyethylene THA does not affect early cup fixation.

7. FUTURE PERSPECTIVES

- The evaluation of dislocation in observational, register-based studies is difficult, because dislocation is multifactorial. So, even if they are well matched and designed for the optimal control of known confounders, they will always suffer from residual confounding. On the other hand, randomized, controlled trials address this issue, but, since dislocations are rare and revisions due to dislocations are even more rare, they will probably suffer from insufficient power. Register-based, randomized, controlled trials could combine the external validity and high statistical power of large datasets with the internal validity of randomization and prospective data collection. These studies might be able to detect clinically relevant differences in dislocation rates between different head sizes and help us identify the optimal head size.

- The question of whether there is a downside to using large heads in THA, in terms of polyethylene wear, fretting and corrosion at the taper-trunnion junction, and compromised cup fixation remains unclear. In this thesis, no association between head size and the abovementioned adverse events was observed in the short perspective. Longer-term results, exceeding 10 years of follow-up, will make it possible to draw more definitive conclusions about the safety of large metal heads in MoVEPE THA.

8. THE PHD CANDIDATE'S CONTRIBUTION TO THE THESIS

Paper I The PhD candidate had a minor contribution in setting the research protocol and formulating the research questions. He received a raw copy of the NARA database, which he refined after applying the selection criteria, in order to determine the final number of included patients. He processed the data and performed the statistical analysis. He interpreted the results, wrote and revised the manuscript, as well as responded to the reviewers' remarks after the submission.

Paper II The PhD candidate had a more active role in setting the research protocol. Based on the experience gained from Paper I, he proposed and implemented the propensity score matching method, in order to reduce bias. He determined, in association with his supervisors, the exposure and the outcome of the study. As in Paper I, he processed the raw NARA database, applied the inclusion and exclusion criteria, matched the sample according to the head size and performed all the statistics. He had a more active role in the interpretation of the results, wrote and revised the manuscript, as well as responded to the reviewers' remarks after the submission. The PhD candidate also wrote the IRB application for Papers I and II.

Papers III-V The G7-RSA study protocol had already been set when the PhD candidate initiated his third-cycle program. He participated in enrolling and operating some of the Swedish patients. He collected their PROM-data preoperatively and at the follow-ups and organized the dataset for all patients, after receiving the RSA-, PROM- and blood-ion data of the Danish cohort. In Papers III and V, he performed the statistical analysis, wrote and revised the manuscripts, as well as interpreted their results. He also responded to the revirerts' remarks. In Paper IV, the first draft of the manuscript was written by Kristine I. Bunyoz. The PhD candidate wrote parts of this manuscript, particularly the patients and methods section, and propose changes to its structure. He also crosschecked the statistics of Paper IV in SPSS and revised the manuscript, after responding to the reviewers' remarks.

9. RELATED ARTICLES NOT INCLUDED IN THE THESIS

- Tsikandylakis G, Mohaddes M, Cnudde P, Eskelinen A, Karrholm J,Rolfson O. Head size in primary total hip arthroplasty. *EFORT Open Rev*. 2018;3:225-231.

- Skoogh O, Tsikandylakis G, Mohaddes M, Nemes S, Odin D, Grant P, Rolfson O. Contemporary posterior surgical approach in total hip replacement: still more reoperations due to dislocation compared with direct lateral approach? An observational study of the Swedish Hip Arthroplasty Register including 156,979 hips. *Acta Orthop*. 2019;90:411-416.

- Tsikandylakis G, Overgaard S, Zagra L,Kärrholm J. Global diversity in bearings in primary THA. *EFORT Open Rev*. 2020;5:763-77.

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